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EFFECT OF ANESTHESIA ON THE BLOOD OXYGEN

I. A STUDY OF THE EFFECT OF ETHER ANESTHESIA ON THE OXYGEN IN THE ARTERIAL AND IN THE VENOUS BLOOD

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The existence of anoxia during anesthesia is indicated clinically by the frequent appearance of cyanosis and experimentally by the observation of a diminished oxygenation [1] of the blood and oxygen consumption.[2] The deleterious effects of anoxia have been emphasized by Haldane [3] and Barcroft.[4] The latter author has classified the anoxias into three groups and discussed the relative dangers of each. Lunsgaard and Van Slyke [5] have shown that cyanosis does not give adequate clinical indications of the degree of anoxia, since it depends on the presence of a certain quantity of reduced hemoglobin in the blood and not on the relative proportions of reduced and oxygenated blood. This sign may occur in a person with polyglobulism with a small alteration in the oxygen saturation, whereas it could not appear in an anemic person except in the presence of advanced asphyxia. Therefore, it is possible for a subclinical anoxia to exist without cyanosis—yet one which would become injurious if prolonged sufficiently. It is evident that a knowledge

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1. (*a*) Ronzoni, E.; Koechig, I., and Eaton, E. P.: Ether Anesthesia: III. Rôle of Lactic Acid in the Acidosis of Ether Anesthesia, J. Biol. Chem. **61**:465, 1924. (*b*) Austin, J. H.; Cullen, G. E., and Gram, H. C.: Blood Electrolyte Changes in Ether Acidosis, ibid. **61**:829, 1924. (*c*) Blalock, A.: Cardiac Output in the Dog During Ether Anesthesia: I. Effect of Ether Anesthesia on the Cardiac Output, Arch. Surg. **14**:732 (March) 1927. (*d*) Fuss, H., and Derra, E.: Zur Frage der Oxydationsverminderung während der Äthernarkose, Arch. f. exper. Path. u. Pharmakol. **156**:64, 1930.

2. Kruse, T. K.: Studies in Narcosis: II. A Method for the Determination of the Respiratory Exchange During Ether Narcosis, J. Biol. Chem. **56**:139, 1923.

3. Haldane, J. S.: Symptoms, Causes, and Prevention of Anoxaemia, and the Value of Oxygen in Its Treatment, Brit. M. J. **2**:65, 1919.

4. Barcroft, J.: Anoxaemia, Lancet **2**:485 (Sept. 4) 1920.

5. Lunsgaard, C., and Van Slyke, D. D.: Cyanosis, Medicine **2**:1, 1923.

of the effect of an anesthetic agent on the oxygenation of the blood may lead to a better and safer anesthesia and to a smoother period of immediate recovery, both of which influence the ultimate convalescence of the patient.

The observations on the effect of ether anesthesia on the oxygenation of arterial and venous blood have not generally been in accord.[1] The investigators, with the exceptions of Fuss and Derra,[1d] have used the usual technic of Van Slyke and Neill [6] for the blood oxygen determinations. Shaw and Downing [7] have shown that this method, in the presence of ether, may give results as much as 15 per cent in excess of true values. Fuss and Derra used a modification of the technic of Van Slyke and Neill which proved accurate within 10 per cent. In the present investigation we have tried to confirm and extend the previous observations on the oxygen in the arterial and in the venous blood during ether anesthesia with an improved technic and with conditions as near the usual ones met in surgical work as possible.

METHODS

Dogs were used in the experiments. The animals were placed in a supine position on an operating board, and under local anesthesia with procaine hydrochloride the right external jugular vein was exposed and a catheter passed to the junction of the venae cavae or the orifice to the right auricle. Anatomic studies showed that this site lies at the level of the fourth interspace. The catheter was used to facilitate sampling arterial and venous blood simultaneously and to avoid the repeated traumas of direct cardiac needle puncture. It was necessary to inject 1.5 mg. of heparin per kilogram of body weight and to leave the catheter filled with a dilute solution of heparin between samplings in order to prevent the blood from clotting in the catheter. Previous to the sampling of venous blood the plunger of the syringe was drawn backward and forward several times to flush the catheter and to mix the blood at the junction of the venae cavae and thus to avoid any errors due to a slip-stream effect. The blood taken from the vicinity of the orifice of the right auricle should be identical for all practical purposes with the venous blood from the right side of the heart.

After a preliminary period during which the dog was allowed to become quiet, simultaneous samples of venous and arterial blood were drawn anaerobically under liquid petrolatum and preserved in an ice bath until the oxygen determinations could be made. The total volume of the samples of blood in each instance was kept below 15 cc., in order to eliminate as much of the effect of loss of blood as possible. The blood pressure was taken after each sampling of arterial blood by means of a mercury manometer. A small three way stopcock at the needle allowed direct connection between the needle and the manometer. The connecting tubing of the manometer was filled previously with physiologic solution of sodium chloride to elevate the mercury to a pressure slightly above the expected blood pressure.

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6. Van Slyke, D. D., and Neill, J. M.: The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, J. Biol. Chem. **61**:523, 1924.

7. Shaw, J. L., and Downing, V.: The Determination of Oxygen in Blood in the Presence of Ether by a Modification of the Van Slyke-Neill Technique, J. Biol. Chem. **109**:405, 1935.

This was done to obviate any change in the blood volume by dilution or loss of blood, as might happen in the cannulation of the artery. The pulse and respiratory rates were recorded.

The animal was then anesthetized, by the open drop method with a cone, to a state suitable for operation and maintained in this state with as little variation as possible. Criteria of the depth of anesthesia were general relaxation and loss of corneal and knee reflexes. Open air passages were insured at all times by inserting a large bore glass tube via the mouth down to the epiglottis. Secretions were removed from the upper respiratory passages as soon as they accumulated.

Second and third samples of blood were taken after thirty minutes and one hour, respectively.

The animals were killed at the end of the experiment by injecting quickly through the catheter 100 mg. of solution of sodium amytal per kilogram of body weight. Death occurred almost instantly. The trachea was exposed and clamped. An immediate postmortem examination of the lungs was made.

RESULTS

Seven experiments were performed. The results of the blood oxygen determinations in these are listed in the accompanying table and shown graphically in charts 1 and 2.

The oxygen capacity of the arterial blood was increased in six of the seven experiments, the greatest elevation noted being 18.7 per cent.

The oxygen content of the arterial blood showed considerable variation but generally tended to increase slightly. The increase in the oxygen content was not proportional to the rise in the oxygen capacity and thereby gave rise to a diminished oxygen saturation.

The oxygen content of the venous blood increased in all experiments, and in one experiment the increase was as great as 50.3 per cent.

The arteriovenous difference was greatly decreased in all instances.

The oxygen saturation of the arterial blood showed a decrease, and the variations in the individual experiments ranged from 0.4 to 15.6 per cent. In one experiment in the group no significant change in the saturation was noted. In two of the experiments, at different time intervals, normal saturation was obtained in one of the samples and a diminished saturation in the other sample.

The oxygen saturation of the venous blood showed an increase, the values tending to become more variable with the duration of the anesthesia.

In spite of the constant attention to maintenance of an even depth of surgical anesthesia with ether, considerable variation occurred, which was reflected to some extent in the values for the blood oxygen. Such criteria as loss of corneal and other reflexes were deceptive, and in some instances it was noted after blood sampling that the animals were not at the desired depth of anesthesia.

Readings on the blood pressure were made in the last four experiments. In two experiments there was a fall of 20 mm. each (a drop of

10 per cent in one experiment and 15 per cent in the other). The respiratory rates showed increases of 68 and 59 per cent, respectively, for the thirty minute and one hour periods. The pulse rates rose 23 and 29 per cent under similar conditions.

There was always a marked prominence of the surface veins, especially the external jugular vein, during the anesthesia.

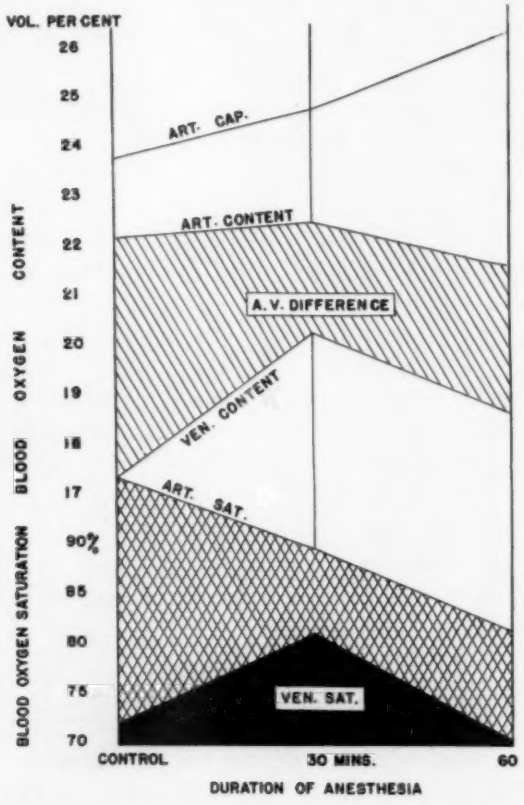

Chart 1.—Blood oxygen determinations in experiment 9.

Eight preliminary experiments were performed, with Fuss and Derra's [1d] modification of the technic of Van Slyke and Neill for the blood oxygen determinations during ether anesthesia. The findings in these conformed generally to the results previously related and were of greater magnitude. Since Shaw and Downing [7] later found that this method gave results varying as much as 10 per cent from the true values, these experiments are not being reported, but they are mentioned at this point because of the accordance with the aforementioned results.

Postmortem examination of the lungs showed a marked variation in the color of the lobes. The upper lobes were usually pink and of

normal appearance. The lower lobes were a bluish gray and frequently showed congestion and marked discoloration in the more dependent portions. After release of the tracheal clamp, scattered areas, from 2 to 3 cm. in diameter, that did not collapse were noted frequently. These areas were less crepitant on palpation than the neighboring lung tissue, and on gross section a clear fluid could be expressed. The lower

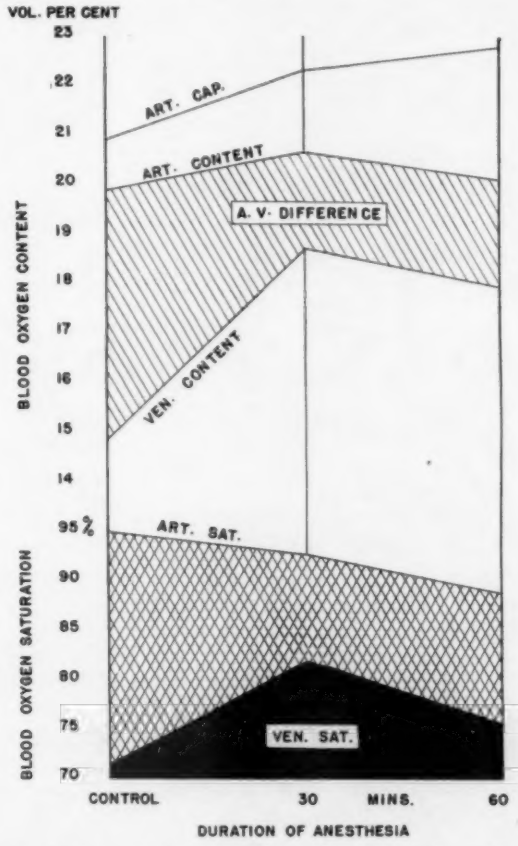

Chart 2.—Mean of the results in the experimental series. The values used in this chart were calculated by using the mean percentile changes for the experimental series and as the control the normal values for human blood as follows: oxygen capacity of arterial blood, 20.9 volumes per cent; oxygen content of arterial blood, 19.9 volumes per cent; oxygen content of venous blood, 14.9 volumes per cent; arteriovenous difference, 5 volumes per cent; oxygen saturation of arterial blood, 95 per cent, and oxygen saturation of venous blood, 71.4 per cent.

lobes generally showed diffuse congestion. Bloody fluid could be expressed from the surface on section. Microscopic sections showed no change, other than dilated capillaries, which suggested congestion.

Oxygen Values in Arterial and in Venous Blood of Dogs Under Ether Anesthesia

Experiment No.	Oxygen Capacity of Arterial Blood			Oxygen Content of Arterial Blood			Oxygen Content of Venous Blood			Arteriovenous Difference			Oxygen Saturation of Arterial Blood*			Oxygen Saturation of Venous Blood*		
	Control Blood	Blood Sample After Anesthesia		Control Blood	Blood Sample After Anesthesia		Control Blood	Blood Sample After Anesthesia		Control Blood	Blood Sample After Anesthesia		Control Blood	Blood Sample After Anesthesia		Control Blood	Blood Sample After Anesthesia	
		30 Min.	1 Hour		30 Min.	1 Hour		30 Min.	1 Hour		30 Min.	1 Hour		30 Min.	1 Hour		30 Min.	1 Hour
	Volumes per Cent	Volumes per Cent	Volumes per Cent	Volumes per Cent	Volumes per Cent	Volumes per Cent	Volumes per Cent	Volumes per Cent	Volumes per Cent	Volumes per Cent	Volumes per Cent	Volumes per Cent	Percentage	Percentage	Percentage	Percentage	Percentage	Percentage
9	23.84	24.80	26.30	22.20	22.50	21.60	17.40	20.34	18.70	4.80	2.76	2.90	92.3	89.9	81.5	72.1	81.2	70.3
10	13.35	13.40	15.80	12.50	13.10	14.25	8.55	10.30	11.30	3.95	2.80	2.95	92.2	96.3	89.5	62.6	75.7	70.2
12	16.50	17.70	17.30	15.80	14.20	16.50	8.35	1.20†	12.75	7.55	13.00†	3.75	94.5	79.0	94.2	49.4	....	72.7
13	19.50	22.50	23.10	18.50	21.10	19.00	13.90	19.70	16.10	4.60	1.40	2.90	93.9	93.0	81.3	70.3	86.7	68.9
14	16.40	18.20	17.85	15.20	8.00‡	16.00	11.22	12.45	13.10	4.00	....	2.90	91.5	43.9‡	88.5	67.2	67.3	72.2
16	17.41	17.80	17.37	16.08	16.80	16.09	11.34	15.80	14.61	4.74	1.00	1.48	91.4	93.3	91.4	64.0	87.7	83.1
17	22.10	.....	22.50	21.90	.....	17.05	17.80	.....	9.60	4.10	....	7.45	98.2	....	75.3	79.7	....	41.8
Mean percentile change for the experimental series.....		+6.70	+8.93		+3.97	+1.05		+25.70	+20.53		−53.95	−26.19		−2.56	−7.49		+12.48	+ 1.96
Mean variation of the mean percentile change§		±5.62	±7.99		±4.96	±9.36		±14.19	±17.77		±23.60	±22.35		±6.59	±7.87		± 8.75	±17.96
Mean of the mean variation of the mean percentile change.....		±2.29	±3.21		±2.22	±3.68		± 6.35	± 6.72		±11.60	± 8.44		±2.94	±2.97		± 1.24	± 6.79

* In the computation of the oxygen saturation of the arterial and of the venous blood, 0.5 and 0.3 volumes per cent were deducted from the oxygen capacity of the arterial blood and the oxygen content of the arterial and the venous blood, respectively, to allow for dissolved oxygen not in combination with the hemoglobin. The oxygen capacity of the arterial blood was used to calculate the oxygen saturation of the venous blood for general comparison, since the oxygen capacity of the venous blood was not determined in all instances.

† Tracheal obstruction (not included in the statistical analysis).

‡ Deep anesthesia (not included in the statistical analysis).

§ Scott, E. L.: What Constitutes an Adequate Series of Physiological Observations? J. Biol. Chem. **73**: 81, 1927.

COMMENT

It is apparent that anesthetization of dogs with ether by the cone drop method produces the following changes:

1. A progressive increase in the oxygen capacity of the arterial blood. This increase is probably a response to anoxia [8] or to adrenal secretion.[9] A reduction in the blood volume due to loss of fluid may contribute but plays a lesser rôle.[10]

2. Equivocal changes or a slight rise in the oxygen content of the arterial blood. The failure of the oxygen content of the arterial blood to rise in a degre parallel with the increase in the oxygen capacity may be due to a number of factors, such as a reduction of the alveolar oxygen tension, a decrease in the permeability of the alveolar and cellular membranes due to the ether, scattered focal edema of the lung tissues and interference with the collateral respiration, an alteration in the respirations and the effect of a lowered p_H on the oxygen-combining power of the hemoglobin.

It is unlikely that ether lowers the oxygen tension of inspired air sufficiently to affect the oxygen content of the arterial blood. Animals are anesthetized surgically when breathing a mixture of ether and air in which the ether exerts a partial pressure of 21 mm.[11] Such a mixture

8. (*a*) Izquierdo, J. J.: Studies on the Conditions of Activity in Endocrine Glands: XXV. The Polycythemia of Acute Anoxemia and Its Relation to the Sympathico-Adrenal System, Am. J. Physiol. **86**:145, 1928. (*b*) Gregg, H. W.; Lutz, B. R., and Schneider, E. C.: Compensatory Reactions to Low Oxygen, ibid. **50**:302, 1919-1920. (*c*) Dallwig, H. C.; Kolls, A. C., and Loevenhart, A. S.: The Mechanism Adapting the Oxygen Capacity of Blood to the Requirements of the Tissues, ibid. **39**:77, 1915. (*d*) Schneider, E. C., and Havens, L. C.: The Changes in the Content of Hemoglobin and Red Corpuscles in the Blood of Man at High Altitudes, ibid. **36**:380, 1914-1915.

9. Kellaway, C. H.: Some Physiological Effects of Anoxaemia, J. Physiol. **52**:lxiii, 1919. Epstein, A. A., and Aschner, P. W.: The Effect of Surgical Procedures on the Blood Sugar Content, J. Biol. Chem. **25**:151, 1916. Atkinson, H. V., and Ets, H. N.: Chemical Changes of the Blood Under the Influence of Drugs: I. Ether, ibid. **52**:5, 1922. Phillips, R. A., and Freeman, N. E.: Ether Hyperglycemia, Proc. Soc. Exper. Biol. & Med. **31**:286, 1933. Lamson, P. D.: The Part Played by the Liver in the Regulation of Blood Volume and Red Corpuscle Concentration in Acute Physiological Conditions, J. Pharmacol. & Exper. Therap. **16**:125, 1920. Edmunds, C. W., and Nelson, E. E.: Factors Concerned in the Polycythemia Produced by the Subcutaneous Injection of Epinephrine, J. Exper. Med. **41**:1, 1925. Izquierdo.[8a] Dallwig, Kolls and Loevenhart.[8c]

10. Eppinger, H., and Schürmeyer, A.: Ueber den Kollaps und analoge Zustände, Klin. Wchnschr. **7**:777 (April 22) 1928. Gasser, H. S.; Erlanger, J., and Meek, W. J.: Studies in Secondary Traumatic Shock: IV. The Blood Volume Changes and the Effect of Gum Acacia on Their Development, Am. J. Physiol. **50**:31, 1919.

11. Haggard, H. W.: The Absorption, Distribution, and Elimination of Ethyl Ether, J. Biol. Chem. **59**:737, 1924.

reduces the partial pressure of the oxygen in the respiratory air only 4 or 5 mm. and would exert an insignificant effect on the oxygenation of arterial blood.[12] However, the use of a cone may cause sufficient rebreathing to reduce the alveolar oxygen tension. In two experiments an improvement of the oxygen saturation of the arterial blood was observed after removal of the cone.

The extent to which ether interferes with the permeability of the cell membrane or the oxygen-carrying capacity of the hemoglobin is subject to conjecture. The fatty constituents of the cell wall compose one of the factors influencing permeability of the membrane.[13] Prolonged exposure of animals to ether anesthesia produces alteration of form and structure of the red blood cells, as well as hemolysis.[14] Thus ether may hinder the absorption of oxygen by the hemoglobin by interfering with its passage through the cell membrane of either the red blood cell or the alveolar capillary epithelium.

The focal edema observed is not of sufficient magnitude to interfere with the collateral respiration,[15] since only a small portion of the lungs was involved. Two thirds of the lungs may be obstructed before the appearance of cyanosis.[5]

Ether anesthesia influences the rate [16] and depth of respiration and then the respiratory exchange. Haldane [3] and Matthes [17] found that the depth of respiration influenced the oxygen saturation of the arterial blood. These respiratory changes alter the respiratory exchange or residual air,[18] thus lowering the alveolar oxygen tension and affecting the oxygen saturation. This is substantiated also by the fact that the severity of the anoxia varied directly, as a rule, with the depth of the anesthesia.

12. Bock, A. V.; Field, H., Jr., and Adair, G. S.: The Oxygen and Carbon Dioxide Dissociation Curves of Human Blood, J. Biol. Chem. **59**:353, 1924.

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17. Matthes, K.: Ueber den Einfluss der Atmung auf die Sauerstoffsättigung des Arterienblutes, Arch. f. exper. Path. u. Pharmakol. **176**:683, 1934.

18. Hurtado, A.; Kaltreider, N. L., and McCann, W. S.: Studies of Total Pulmonary Capacity and Its Sub-Divisions: IX. Relationship to Oxygen Saturation and Carbon Dioxide Content of Arterial Blood, J. Clin. Investigation **14**:94. 1935.

The acidosis accompanying ether anesthesia[19] may depress the p_H sufficiently to lower the extent of dissociation of hemoglobin and thereby the oxygen content of the arterial blood.[20]

3. Elevation of the oxygen content of the venous blood. This transpires as the result of, primarily, an increased velocity in the flow of blood arising from dilatation of the peripheral arterioles[16] and an increased cardiac output;[21] secondarily, the histotoxic influence of the ether on cellular metabolism,[22] and finally, the diminished blood oxygen tension. The distention of the peripheral veins, evidence of pulmonary congestion and increased cardiac output, contributes further evidence of an accelerated flow of blood from artery to vein. The blood is therefore not in contact with the tissues for a period of time sufficient for removal of oxygen.

4. A decrease in the arteriovenous difference. This is the result of an elevation of the oxygen content of the venous blood, thereby causing it to approach the content of the arterial blood.

5. An increase in the oxygen saturation of the venous blood. This is a consequence of the elevation of the oxygen content of the venous blood.

6. A decrease in the oxygen saturation of the arterial blood. This is indicative of anoxic anoxia. No attempt was made experimentally to determine the responsible factors. It is probable that, of the several factors previously mentioned, altered respiration, lowered p_H of the blood and the effect of ether on the permeability of cell membranes play the most prominent rôles. In anoxic anoxia the blood oxygen tension is lower than normal, and for this reason Barcroft stated that it is the most dangerous of all anoxias.[4] Since the oxygen tension determines the pressure differential, i. e., the rate of diffusion across tissue spaces, the oxygen of the blood is not adequately available to the body tissues. Barcroft's experiences in the low pressure oxygen chamber show that, though the oxygen content of his blood was the same before as after breathing the rarefied air, he suffered effects of anoxia.

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19. Van Slyke, D. D.; Austin, J. H., and Cullen, G. E.: The Effect of Ether Anesthesia on the Acid-Base Balance of the Blood, J. Biol. Chem. **53**:277, 1922. Cullen, G. E.; Austin, J. H.; Kornblum, K., and Robinson, H. W.: The Initial Acidosis in Ether Anesthesia, ibid. **56**:625, 1923.

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21. Blalock, A.: Cardiac Output in Dogs During Ether Anesthesia: Effect of Ether Anesthesia on Cardiac Output, Arch. Surg. **14**:732 (March) 1927.

22. Brow, G. R., and Long, C. N. H.: Biochemical Changes in the Heart Muscle During Anesthesia, Anesth. & Analg. **9**:193, 1930.

The subjection of a patient to anoxia for the duration of an operation adds additional trauma to that induced by the surgical procedures. In addition to the toxic effects of the anesthetic agent, it leads to the accumulation of metabolites in the cells as a result of impaired oxidation.[23] This may cause an injury to the cells, the repair of which requires a longer time than the action of its precipitating factor—probably extending over into the postoperative period of recovery—and may be a determining factor in the smooth or stormy postoperative convalescence. In subjects of low reserve such additional trauma may precipitate a break in metabolic compensation terminating in shock.[24]

The histotoxic effect of the anesthetic agent cannot be avoided, but the anoxia may be mitigated by adding oxygen to the respiratory mixture, thus insuring complete oxygen saturation of the arterial blood, and thereby increasing the availability of oxygen.

SUMMARY

Ether anesthesia induced in dogs by the cone drop method causes the following changes: (1) a decrease in the oxygen saturation of the arterial blood; an increase in the oxygen capacity of the arterial blood; equivocal changes, though usually a slight increase, in the oxygen content of the arterial blood; an increase in the oxygen content of the venous blood, and a decrease in the arteriovenous blood oxygen difference; (2) scattered areas of pulmonary edema with congestion in the more dependent portions of the lung.

CONCLUSION

The findings reported indicate the existence of an anoxic anoxia in subjects under ether anesthesia induced by the cone drop method. It is suggested that oxygen be administered coincidentally, in order to insure a normal oxygen saturation of the arterial blood.

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23. Koehler, A. E.; Brunquist, E. H., and Loevenhart, A.: The Production of Acidosis by Anoxemia, J. Biol. Chem. **64**:313, 1925. Barcroft, J., and Orbeli, L.: The Influence of Lactic Acid upon the Dissociation Curve of Blood, J. Physiol. **41**:355, 1910-1911.

24. Freeman, N. E.; Shaw, J. L., and Snyder, J. C.: The Peripheral Blood Flow in Surgical Shock: The Reduction in Circulation Through the Hand Resulting from Pain, Fear, Cold, and Asphyxia, with Quantitative Measurements of the Volume Flow of Blood in Clinical Cases of Surgical Shock, J. Clin. Investigation **15**:651, 1936.

CANCER OF THE DUODENUM

A CLINICAL AND ROENTGENOGRAPHIC STUDY OF EIGHTEEN CASES

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Since Hamberger [1] reported the first case of carcinoma of the duodenum in 1746, an extensive literature has accumulated, out of all proportion to the number of cases which have occurred. Little has been written, however, on the roentgenographic picture of the disease. This paper presents the results of a clinical and roentgenographic study of 18 cases of primary carcinoma of the duodenum, in 5 of which the patient was personally examined and studied during life by us. The data on these cases have been collected from seven different hospitals and have not been previously reported.

INCIDENCE

The rarity of primary cancer of the duodenum is shown by the following figures compiled from the statistics of various authors. The incidence of primary carcinoma of the duodenum in 350,286 autopsies was 0.033 per cent. Perry [2] in 17,652 autopsies performed at Guy's Hospital found 6 primary sarcomas of the duodenum, from which figures the incidence of sarcoma would appear to equal that of carcinoma, namely, 0.033 per cent. This figure is probably far too high and is not generally accepted. In the material at our hospitals there were no sarcomas of the duodenum.

Cancer of the duodenum constitutes only 0.3 per cent of cancers of the intestine. Of 228 cancers of the small intestine, 104 (45.6 per cent) were located in the duodenum and 124 (54.3 per cent) involved the jejunum and the ileum. It is thus evident that nearly one half

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From the Memorial Hospital for the Treatment of Cancer and Allied Diseases, the New York Polyclinic Medical School and Hospital, the New York Post-Graduate Medical School and Hospital, the Lenox Hill Hospital and St. John's Long Island City Hospital, all of New York; the Paterson General Hospital, Paterson, N. J., and the New Haven Hospital, New Haven, Conn.

1. Hamberger, G. E.: De ruptura intestini duodeni, Jena, Ritterianis, 1746; in Haller, A.: Disputationes ad morborum historiam et curationem facientes, Lausanne, M. M. Bousquet et soc., 1757, vol. 3, p. 507.

2. Perry, E. C.: Papilloma of the Duodenum, Tr. Path. Soc. London **44**:84, 1892-1893.

of the carcinomas of the small intestine are in the short length of the duodenum, justifying Jefferson's [3] statement that "inch for inch the duodenum is more likely to undergo cancerous change than the jejunum or ileum." Of the whole small intestine the duodenum appears to be the only place where carcinoma predominates, so that three fourths of the carcinomas of the small intestine occur in the duodenum. This is supported by Tuttle's [4] analysis of 2,432 malignant tumors of the intestine, in which he found carcinoma as follows: Of 37 cancers of the ileum, 15 were carcinomas and 22 were sarcomas; of 14 cancers of the jejunum, 2 were carcinomas and 12 were sarcomas; of 8 cancers of the duodenum, 7 were carcinomas and only 1 was a sarcoma.

AGE AND SEX INCIDENCE

Carcinoma of the duodenum occurs most frequently in the sixth decade of life and is rare before the age of 40. Ewald [5] reported a case in a 16 year old boy. Whittier [6] in 1889 reported a case in a patient aged 17 years and 2 cases in patients 18 years of age. The youngest patient in our series was an 18 year old boy; the oldest patient, a man of 78 years. The average age of our patients was 53 years. Most authors agree that the sex incidence reveals a preponderance of males of 3:1. The ratio varies widely among writers, as would be expected, since most reports include only small numbers of cases. This is clearly shown in our series of 18 cases, 12 of which were in females and 6 of which were in males, making a preponderance of females of 2:1. The series of 15 cases from the Mayo Clinic, reported by Eusterman, Berkman and Swan,[7] showed a preponderance of males of 4:1.

ETIOLOGY

Theories concerning the etiology are many, and no single one applies to all cases. They include: the supervention of cancer on chronic duodenal ulcer, irritation of the alkaline currents from the ducts of the pancreas and biliary system and also by the acid gastric contents, the presence in the duodenum of aberrant thyroid or pancreatic tissue, transition of junctional epithelium at the termination of the ducts,

3. Jefferson, G.: Carcinoma of the Suprapapillary Duodenum Causally Associated with Pre-Existing Simple Ulcer: Report of a Case and an Appendix of Thirty Collected Cases, Brit. J. Surg. **4**:209, 1916-1917.

4. Tuttle, J. P.: Carcinoma of the Intestinal Tract, M. Rec. **68**:728, 1905.

5. Ewald, C. A.: Ein Fall von Atrophie der Magenschleimhaut mit Verlust der Salzsäuresecretion: Ulcus carcinomatosum duodenale, Berl. klin. Wchnschr. **25**:527, 1886.

6. Whittier, E. N.: Primary Malignant Disease of the Duodenum, Tr. A. Am. Physicians **4**:292, 1889.

7. Eusterman, G. B.; Berkman, D. M., and Swan, T. S.: Primary Carcinoma of the Duodenum: Report of Fifteen Verified Cases, Ann. Surg. **82**:153, 1925.

origin in aberrant gastric glands and the degeneration of a previously benign lesion, such as a polyp, adenoma, papilloma or diverticulum.

If chronic irritation is a factor in the causation of carcinoma of the duodenum, the biliary papilla or the ampulla of Vater should be a frequent site for its development, since, as Cohen and Colp [8] have pointed out, this structure projects into the lumen of the intestine and is subject to the irritation of the eddying alkaline currents from the ducts and the acid wash of the gastric contents. Evidence of the importance of this factor may be found in the fact that cancers of the second portion of the duodenum constitute nearly two thirds of all carcinomas. The frequency of carcinoma in the three divisions of the duodenum is approximately as follows: supra-ampullary, 24.9 per cent; periampullary, 61.9 per cent, and infra-ampullary, 13.1 per cent.

A theory which has provoked much discussion is one that carcinoma may arise in the scar of a chronic duodenal ulcer. Jefferson [3] collected reports of 30 such cases and concluded that a certain number were doubtful examples of duodenal carcinoma arising from duodenal ulcer and that a causal relationship between simple ulcer and carcinoma of the duodenum was difficult to establish. Eichhorst [9] reported a case of duodenal ulcer after burning, with the unusual end-result of carcinomatous degeneration around the periphery and a metastatic nodule from the duodenum developing in the thoracic portion of the spine. Schofield [10] concluded that "in view of the frequency of duodenal ulcer it is remarkable that duodenal cancer should be so rare. Further, cancer of the duodenum is most frequent in the region of the ampulla, while ulcer is practically confined to the supra-ampullary region of the duodenum." Hinton [11] in 1931, after carefully examining the evidence, concluded that "clinically one can disregard the possibility of a duodenal ulcer ever taking on malignant degeneration."

In this connection it is of interest that in only 1 of our cases did the history suggest preceding duodenal ulcer (case 6). For some reason as yet unexplained, gastric mucosa is much more susceptible to the development of cancer than is duodenal mucosa, for several cases are on record in which a duodenal ulcer extended through the pylorus and became malignant in the gastric portion only. Sherron reported 2 cases in which gastro-enterostomy was performed for simple ulcer, and when the abdomen was reopened a year later, the duodenal portion of the

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8. Cohen, I., and Colp, R.: Cancer of the Peri-Ampullary Region of the Duodenum, Surg., Gynec. & Obst. **45**:332, 1927.

9. Eichhorst, H. L.: Handbuch der speciellen Pathologie und Therapie, ed. 4, Leipzig, Urban & Schwarzenberg, 1890, vol. 2, p. 234.

10. Schofield, J. E.: Carcinoma of the Duodenum, Brit. J. Surg. **18**:84, 1930.

11. Hinton, J. W.: Does Carcinoma of Duodenum Ever Arise from Duodenal Ulcers? Report of Cases, Am. J. M. Sc. **181**:843, 1931.

ulcer was found to be healed while the intragastric portion had become malignant. W. J. Mayo [12] has reported several similar cases.

PATHOLOGIC PICTURE

The pathologic picture of carcinoma of the duodenum resembles that of carcinoma elsewhere throughout the intestinal tract. The usual type is some variety of cylindric cell adenocarcinoma arising from the mucosa of the duodenum (fig. 11). Three gross forms preponderate: (1) a scirrhous annular tumor with few cells and abundant stroma; (2) a bulky polypoid mass of soft consistence, often showing necrosis and ulceration, made up of abundant cells and little stroma (figs. 10, 15, 20 and 24), and (3) a hard elastic tumor of the colloid type, showing mucoid degeneration.

In all three types obstruction of the lumen usually occurs (figs. 7, 14, 15, 17 and 26). The tumor may remain superficial and cause obstruction by reason of its bulk, or it may infiltrate the wall and invade the head of the pancreas (fig. 7). When this has occurred, careful study is required to distinguish the exact site of origin so as to differentiate it from a primary carcinoma of the head of the pancreas.

Although any of the foregoing types may be found anywhere in the duodenum, it appears to be true that the hard, fibrous type is found more often in the supra-ampullary portion. Tumors of the periampullary region are frequently of the soft, bulky, polypoid variety with a marked tendency to ulceration and bleeding. Carcinomas of the infra-ampullary portion most often consist of broad, flat, ulcerating masses. However, the bulkiest tumors in our series occurred in this region close to the ligament of Treitz.

The outstanding feature of carcinoma of the duodenum is its tendency to cause obstruction of the duodenum and the neighboring structures. As the obstruction increases, there occur compensatory thickening and hypertrophy of the muscular coat, followed by dilatation of the duodenum, pylorus and stomach and chronic catarrhal inflammation of the mucous membranes (figs. 14 and 26), perhaps with superficial ulceration (Brill [13]). When the tumor arises in the periampullary region close to the papilla of Vater, the severe symptoms of obstruction of the bile and pancreatic ducts bring the patient to exploratory operation, as a rule, before the obstruction of the duodenum and stomach have progressed to the stage of marked pathologic change. The bile ducts and pancreatic ducts may be greatly dilated (fig. 15).

12. Mayo, W. J.: A Case of Carcinoma of the Duodenal End of the Common Duct with Successful Excision, St. Paul M. J. **3**:374, 1901.

13. Brill, N. E.: Primary Carcinoma of the Duodenum, Am. J. M. Sc. **128**: 824, 1904.

Jaundice is extreme, the gallbladder may be distended and there may be suppurative disease of the biliary and pancreatic systems, with abscess formation, fat necrosis and ascites.

Because of the rapid evolution of the disease, due to the interference with such essential functions as those of the liver, pancreas and gastrointestinal tract, metastasis is not commonly found at operation or even at autopsy. Outerbridge [14] collected reports of 125 cases and found metastases in only 27 (20 per cent). In our 18 cases, metastases occurred in only 6, or 33.3 per cent. The primary tumors in these cases were distributed throughout all portions of the duodenum. The metastases were found in the regional lymph nodes, liver, pancreas, transverse mesocolon, ileocecal junction and parietal and visceral peritoneum. None of these metastases were large, probably because of the rapid course of the disease. Metastases to the lungs, supraclavicular nodes, gallbladder and bones have also been reported.

Since carcinoma of the duodenum arises from the mucosa of the intestine, its microscopic appearance usually is that of some type of cylindric cell adenocarcinoma. The grading varies from a low grade malignant adenoma (fig. 11) to a highly cellular, anaplastic tumor revealing no evidence of glandular origin or of alveolar formation (fig. 8). Occasionally, areas of squamous metaplasia may be found. Of 17 specimens obtained in the 18 cases reported here, 3 were classified as malignant adenoma and 14 as adenocarcinoma. A carcinoma of the ampulla of Vater is not a true duodenal cancer since it rises in the epithelium lining the terminal portion of the bile duct. The growth usually exhibits the histologic characteristic of the epithelium of the bile duct and may even develop into a true epidermoid carcinoma (fig. 1).

SYMPTOMS

The symptoms of cancer of the duodenum are usually discussed separately, according to the three divisions of the duodenum in which the growth may be located. Kellogg and Kellogg [15] pointed out that there are two sets of symptoms of duodenal cancer. One group includes a large number of symptoms common to all parts of the duodenum affected, while the second group comprises a small number of differential signs varying with the location of the growth. Similarly, Eger [16] pointed out that the chief symptoms of malignant tumors of the duo-

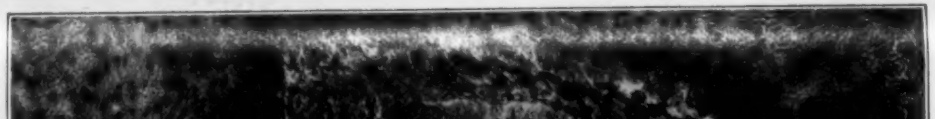
14. Outerbridge, G. W.: Carcinoma of the Papilla of Vater, Ann. Surg. **62:** 402, 1913.

15. Kellogg, E. L., and Kellogg, W. A.: Tumors of the Duodenum, Am. J. Surg. **19:**268, 1933.

16. Eger, S. A.: Primary Malignant Disease of the Duodenum, Arch. Surg. **27:**1087 (Dec.) 1933.

TABLE 1.—*Summary of Pathologic Data of Primary Carcinoma of Duodenum*

Patient	Location of Growth	Gross Type	Microscopic Type	Metastases	Secondary Pathologic Changes
M. B.	Supra-ampullary, 2 cm. distal to pylorus	Hard; ulcerated mass; 4 cm. in diameter, obstructing lumen	Malignant adenoma	Lymph nodes, pancreas and transverse mesocolon, posterior cul-de-sac and ileocecal junction	Bilateral acute parotitis; dilatation of stomach; recent tracheotomy
D. H.	Infra-ampullary, near duodenojejunal junction	Spheroidal, firm, opaque, partly necrotic tumor arising from third portion of duodenum, causing partial obstruction; 2 cm. in diameter	Primary cellular anaplastic radiosensitive adenocarcinoma	None	Dilatation of stomach; acute parenchymatous degeneration of liver; radiation necrosis of tumor
B. K.	Supra-ampullary	Bulky tumor, 6 by 4 cm., obstructing lumen	Primary malignant adenoma	None	Imperfect closure of duodenum with fistula; focal and pelvic peritonitis; bronchial pneumonia
C. S.	Periampullary, 10 cm. distal to pylorus	Bulky, ulcerated, papillary growth involving whole circumference and extending 6 cm. along lumen, involving ampulla	Primary malignant adenoma	.....	Dilatation of stomach, first portion of duodenum, common bile duct and gallbladder; extreme jaundice
L. H.	Supra-ampullary, 2 cm. from pylorus	Ulcer with necrotic edges and base	Adenocarcinoma, containing areas of anaplastic squamous epithelium	None	Dilatation of stomach; diverticulosis of colon; interstitial nephritis
M. B.	Infra-ampullary at duodenojejunal junction	Bulky, polypoid, ulcerated, soft mass invading duodenal wall and obstructing lumen over distance of 11 cm.	Small cell adenocarcinoma	None	Moderate jaundice; stomach and duodenum markedly dilated
H. S.	Supra-ampullary	First and second portions of duodenum involved by hard, whitish, elastic tumor tissue, grossly malignant	No biopsy material obtained; not verified histologically	None	No autopsy
C. A.	Periampullary	Hard tumor invading head of pancreas from primary site in duodenum	Adenocarcinoma of Brunner's glands	Pancreas	Moderate jaundice; extreme dilatation of stomach, common bile duct and gallbladder; cholelithiasis; toxic hepatitis
H. B.	Infra-ampullary, 2 cm. above duodenojejunal junction	Indurated, ulcerated tumor obstructing lumen	Adenocarcinoma, arising from glands of Lieberkuhn	None	Generalized peritonitis; acute exudative pleuritis; hypostatic pneumonia
A. B.	Infra-ampullary, 8 cm. from pylorus	Broad, annular, papillary and infiltrating tumor, 8 cm. in length; ulcerated; invades wall	Papillary adenocarcinoma, grade 2	Regional nodes, liver and pancreas, visceral and parietal peritoneum	Dilatation of duodenal cap and pylorus; toxic cirrhosis of liver; ascites
S. A.	Periampullary	Bulky, firm tumor obstructing lumen of duodenum and bile duct; tumor measured 4 by 3 by 2 cm.	Primary cellular adenocarcinoma	None	Dilatation of common duct and gallbladder
E. D.	Periampullary	Soft, polypoid tumor surrounding ampulla of Vater	Papillary adenocarcinoma	None	Obstruction of bile duct, dilatation of gallbladder, marked jaundice; bronchopneumonia
J. R.	Infra-ampullary	Bulky, friable tumor obstructing terminal portion of duodenum	Adenocarcinoma	Multiple metastases in liver	Lived 2 yr.; no autopsy
W. J. F.	Infra-ampullary	Broad, flat, infiltrating tumor obstructing terminal portion of duodenum	Adenocarcinoma	Numerous metastases in liver and generalized carcinomatosis of all abdominal organs	
F. K.	Periampullary	Friable, fungating tumor surrounding ampulla 3 cm. in diameter	Adenocarcinoma	Metastases to nodes and extension into pancreas	Extreme emaciation; jaundice; stomach and duodenum distended to four times normal size
A. B.	Periampullary	Small, soft friable tumor close to ampulla	Adenocarcinoma	No metastases	
G. M. B.	Infra-ampullary	Bulky, friable tumor obstructing terminal portion of duodenum	Adenocarcinoma	No metastases	No autopsy
C. G.	Periampullary	Soft ulcerated polypoid tumor 2.5 cm. in diameter surrounding ampulla	Adenocarcinoma	None	Jaundice, emaciation, massive hemorrhage in duodenum and in peritoneal cavity and behind peritoneum; enlarged liver, dilated bile and pancreatic ducts



denum depend on obstruction of the duodenal lumen and that they vary more with the rapidity of development and the consistence of the growth than with the location of the tumor, except when it arises from or close to the papilla of Vater and causes symptoms of biliary obstruction, with or without evidence of intestinal obstruction. With this

Fig. 1.—Section of a carcinoma of the ampulla of Vater. This is not a true duodenal cancer since it arises in the epithelium lining the terminal portion of the bile duct.

exception and the presence of bile and pancreatic juice in the vomitus (when the obstruction is distal to the ampulla of Vater), all three portions of the duodenum when obstructed produce the same symptoms.

The first symptoms of duodenal obstruction are usually referable to the stomach. In the early stages these include loss of appetite, gaseous

eructations, epigastric distention and occasional nausea. As obstruction develops, these symptoms increase in severity and to them are added pain in the upper portion of the abdomen, vomiting, dehydration, loss of weight and strength and constipation. When in the case of a soft papillary tumor ulceration and sloughing occur, the obstruction may be temporarily relieved and remissions in the severity of symptoms thus brought about.

The pain of cancer of the duodenum varies with the location of the tumor. With lesions of the supra-ampullary and infra-ampullary portions it is a fairly consistent finding. It may be sudden or gradual in onset and dull, sharp, burning or cramplike. As obstruction increases

Fig. 2.—Benign pedunculated adenoma of the pylorus prolapsing into the duodenum, simulating a polypoid tumor of the duodenum.

and the powerful peristaltic efforts of the stomach distend the duodenum, the pain resembles that of pyloric obstruction in its periodicity, crescendo character, relation to the intake of food and relief after vomiting. In certain cases, however, it may have no relation to meals and may not be relieved by vomiting. Cancer of the periampullary portion of the duodenum, with its swift onset of jaundice and its short, rapid course, is often accompanied by pain. Of the 18 cases reported in this series, 17 were featured by pain in the epigastrium and the right side of the hypochondrium.

Vomiting was present in 11 cases in this series. In 7 cases it was absent throughout the whole course. The amount of the vomitus varies with the location of the tumor, the degree of the obstruction and the amount of fluid intake. When the lesion is so located and so advanced

that it obstructs not only the duodenum but the bile and pancreatic ducts as well, the amount of vomitus may be extremely large, and a loss of from 10 to 15 pints (4,800 to 7,200 cc.) daily may not be unusual. The vomitus may be blood stained, diffusely red, brown, black, yellow or green. It may rarely contain frank blood from a brisk hemorrhage, but more often it is the typical coffee-ground vomitus of a slowly bleeding ulceration.

Constipation is usually present after the symptoms of obstruction have developed. This is particularly true if there is biliary obstruction with the production of pale or clay-colored stools. When the obstruction is above the papilla of Vater, the stools are diminished in amount

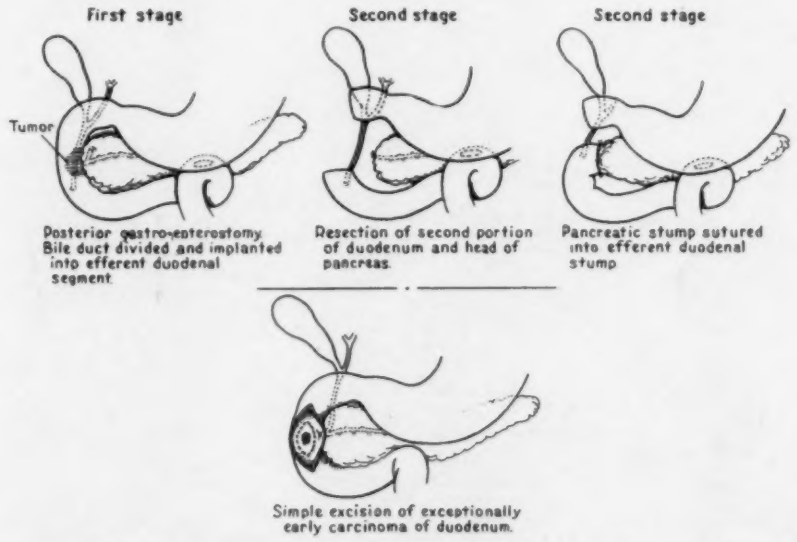

First stage
Second stage
Second stage
Tumor
Posterior gastro-enterostomy. Bile duct divided and implanted into efferent duodenal segment
Resection of second portion of duodenum and head of pancreas
Pancreatic stump sutured into efferent duodenal stump
Simple excision of exceptionally early carcinoma of duodenum

Fig. 3.—Operative procedures used in the treatment of carcinoma of the periampullary portion of the duodenum.

because of the failure of the gastric contents to reach the intestines. Depending on the absence or presence of biliary obstruction and ulceration, the stools may be normal, clay colored or tarry. Stools were examined in 13 cases. In 3 instances tests for occult blood gave positive results. In 8 cases the stools were clay colored, and bile could not be demonstrated by the ordinary tests.

Jaundice occurs when the bile passages are obstructed. Its occurrence is therefore dependent on the location of the growth. A lesion of the periampullary portion produces early, progressive jaundice, which usually is unremitting and painless and may reach an extreme degree (fig. 14). The jaundice may entirely disappear or be intermittent for the following reasons: (1) a soft, friable tumor in this location may

ulcerate and slough away, accompanied by a temporary or lasting relief of the jaundice; (2) increased intrabiliary pressure may force the bile through the obstructed papilla (Brill); (3) the subsidence of papillary edema may release the obstruction and afford relief (Meyer and Rosenberg [17]). When the neoplasm is located in either of the other two portions of the duodenum, jaundice is a late symptom due to extensive damage to the liver by metastatic deposits, to compression of the bile duct by enlarged adjacent lymph nodes or by the direct extension of the growth from its original site to the region of the papilla. Jaundice occurred in 8 of the 18 cases in this series, and it is of interest to note that in 7 of these the tumor originated in the periampullary portion and in 1 in the infra-ampullary portion.

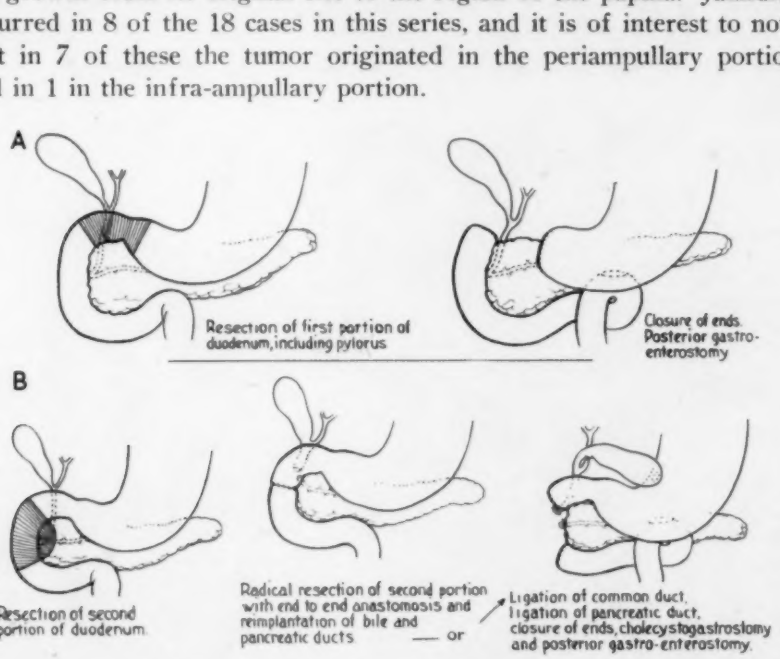

A
Resection of first portion of duodenum, including pylorus
Closure of ends. Posterior gastro-enterostomy
B
Resection of second portion of duodenum
Radical resection of second portion with end to end anastomosis and reimplantation of bile and pancreatic ducts
— or
Ligation of common duct, ligation of pancreatic duct, closure of ends, cholecystogastrostomy and posterior gastro-enterostomy

Fig. 4.—*A*, operative procedures used in the treatment of carcinoma of the supra-ampullary portion of the duodenum, and *B*, operative procedures used in the treatment of carcinoma of the periampullary portion.

Fever usually accompanies biliary obstruction and is not, therefore, an early symptom. It is particularly prevalent when the lesion is of the second portion of the duodenum and is consistent in its association with jaundice, secondary biliary infection and extensive, ulcerated lesions. In the late stages it is a part of the terminal toxemia. In 7 of our cases the elevation of temperature ranged from 1 to 8 F. In 6 of these the lesion was in the second portion of the duodenum and in the seventh it involved the first portion.

17. Meyer, J., and Rosenberg, D. H.: Primary Carcinoma of the Duodenum, Arch. Int. Med. **47**:917 (June) 1931.

The duration of symptoms before diagnosis varies directly with the rapidity of growth of the tumor and also with its location. A tumor of the supra-ampullary or of the infra-ampullary portion causes symptoms of obstruction of the lumen of the duodenum, and the time elapsing between the appearance of the first symptom and the diagnosis in the 4 cases of cancer of the supra-ampullary portion in our series varied between five weeks and nine months and averaged a little more than four months. The interval in 7 cases of cancer of the infra-ampullary portion ranged from six weeks to two years, with an average of slightly more than eleven months. When the lesion arises close to the ampulla, the severity of symptoms increases rapidly. The average

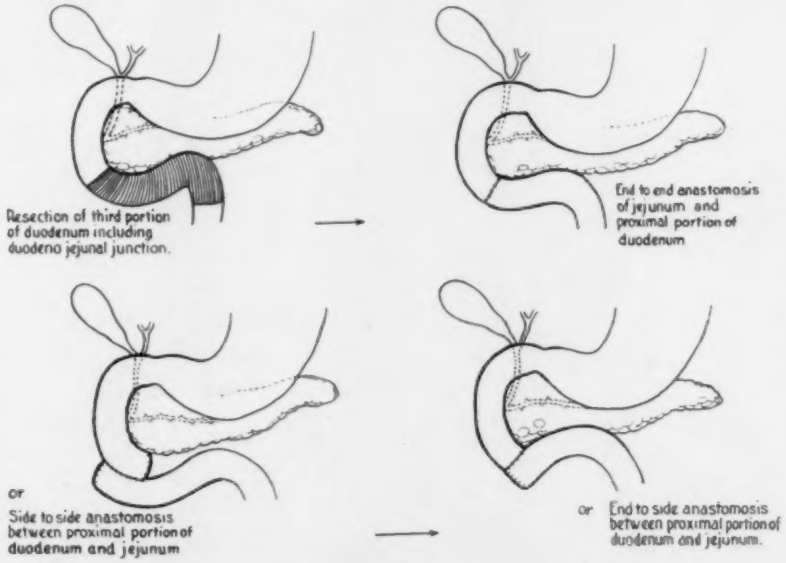

Resection of third portion of duodenum including duodeno jejunal junction.
End to end anastomosis of jejunum and proximal portion of duodenum
or
Side to side anastomosis between proximal portion of duodenum and jejunum
or End to side anastomosis between proximal portion of duodenum and jejunum.

Fig. 5.—Operative procedures used in the treatment of carcinoma of the infra-ampullary portion of the duodenum.

interval in 5 such cases was only eight weeks; in the 2 remaining cases of carcinoma of the periampullary portion symptoms were present for one year before the diagnosis was made.

GENERAL PHYSICAL FINDINGS

The general appearance of the patient suffering with cancer of the duodenum will vary with the duration and the extent of the disease and with the morbid changes produced by the interference with normal processes. Patients in whom complete obstruction has not yet occurred may be in relatively better physical condition than are those in whom obstruction of the duodenum is complete. The skin may be pale or jaundiced. The jaundice may vary from a faint suggestion to an

intensely deep brown. If vomiting has been severe, the evidence of dehydration and cachexia will be obvious in the dry, shriveled tongue and skin. The abdomen is usually flat or even scaphoid. Rarely, ascites may be present. Visible peristaltic waves may course transversely across the epigastrium synchronously with the bouts of pain and call attention to the greatly distended stomach (fig. 14), which is often visible or easily outlined by percussion. Auscultation may disclose gurgling of gas through the tumor, a friction rub of local peritonitis (Eger) and more commonly a gastroduodenal succussion splash, which was found to be present in 4 of the 15 cases at the Mayo Clinic. The loss of weight

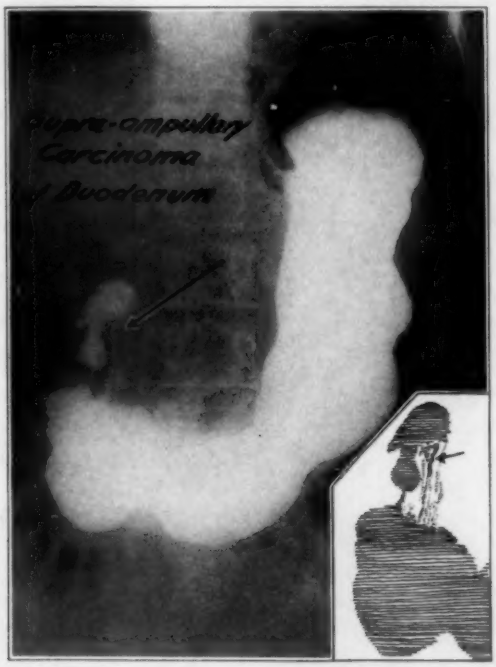


Fig. 6 (case 1).—Carcinoma of the supra-ampullary portion of the duodenum. The picture shows irregularity and narrowing of the base of the duodenal bulb, suggesting contraction produced by chronic ulcer scars. Autopsy showed the deformity to be due to carcinoma.

may be extreme; as much as one fourth of the body weight may be lost in the few months preceding examination. All of our patients had lost considerable weight; one woman had lost 40 pounds (18.1 Kg.) in less than four months (case 7). The loss of weight, as would be expected, was most marked in the group of patients with cancer of the periampullary portion of the duodenum who had a combination of duodenal and biliary obstruction.

Because of this great loss of weight, a palpable mass may be easily outlined in from one third to two thirds of cases. In 10 of our 18 cases (55.5 per cent) a mass was palpated prior to operation. The mass was usually small and relatively fixed in position. The extremes of size were 5 and 12 cm. in diameter. In 3 cases the mass was freely movable, and in each instance it was located in the supra-ampullary portion. In the remaining 7 cases the tumor was located in the second or third portions of the duodenum and was immobile, probably by reason of the peritoneal fixation of these portions of the duodenum to the posterior wall of the abdomen. The masses, therefore, are fairly constant in

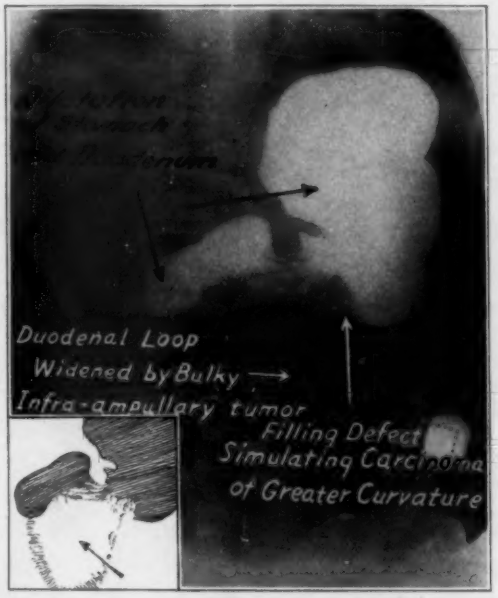


Fig. 7 (case 2).—Bulky carcinoma of the infra-ampullary portion of the duodenum. Note the filling defect on the greater curvature of the stomach, widening of the duodenal loop and retention of barium in the stomach and duodenum.

position, usually in the right half of the epigastrium, in the right side of the hypochondrium or near the umbilicus.

In accordance with Courvoisier's law, the gallbladder may be enlarged, particularly if jaundice is present, but may not be palpated because of an enlarged overlying liver. The liver is usually firm and smooth, but if metastases have occurred it may be nodular. Similarly, peritoneal implantations or greatly enlarged lymph nodes may be palpated.

LABORATORY AND OTHER STUDIES

As Eger pointed out, studies of the blood in the early stages of the disease throw little light on the diagnosis. Later, after the onset of

vomiting or other complications, they are of more value, at least in determining the severity of the disease. As the result of the obstruction and vomiting, toxemia is severe. Dehydration, shock, uremia and tetany-like manifestations are noted. The changes in the blood may include secondary anemia, moderate leukocytosis, a rise in the blood

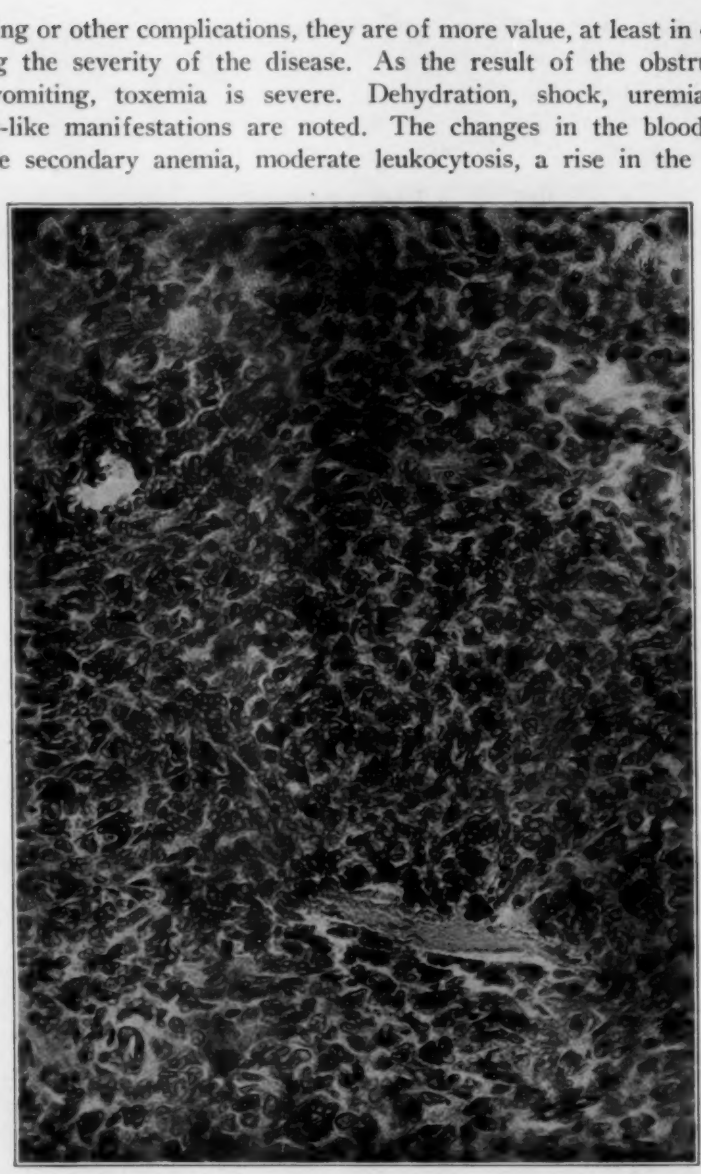


Fig. 8 (case 2).—Microscopic section of the carcinoma demonstrated in figure 7, showing cellular anaplastic adenocarcinoma. (This growth proved remarkably sensitive to a moderate amount of roentgen therapy.)

urea content, a fall in the plasma chloride content, a rise in the carbon dioxide-combining power and a tendency to alkalosis. Alkalis are, therefore, contraindicated; sodium chloride, dextrose and water by the intravenous route constitute the accepted measures.

Analyses of the gastric content furnish information of the highest value. Gross or occult blood is usually present. The analysis may reveal paradoxical findings. With apparently good evidence of a carcinoma of the pylorus one may find normal gastric acidity (case 1). On the other hand, free hydrochloric acid may be diminished or even absent, further confusing the picture. In 5 of the 12 cases reported by Eusterman there was achlorhydria and in 7 diminished amounts of free hydrochloric acid. The finding of bile and pancreatic juice in the gastric contents or vomitus, due to distal obstruction and reverse peristalsis, is a valuable point in differentiating between carcinoma of the infra-ampullary, periampullary and supra-ampullary portions of the duodenum.

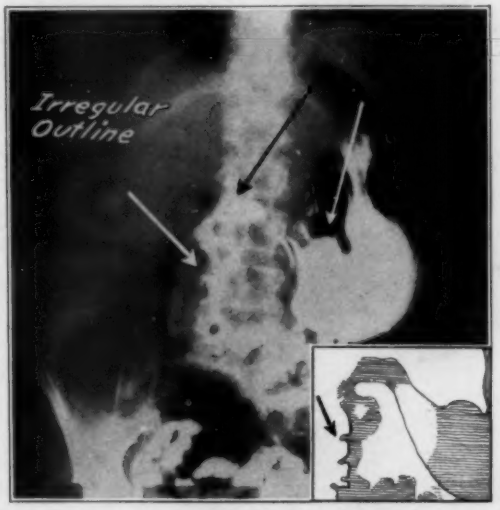


Fig. 9 (case 3).—Roentgenogram made six hours after a barium meal, showing a pressure defect on the greater curvature of the stomach made by a mass in the second portion of the duodenum. Note the irregularity and obstruction of the duodenum with the retention of barium in the stomach and duodenum.

Duodenobiliary drainage is a helpful measure to differentiate jaundice due to malignant obstruction, involving the lower portion of the biliary tract, from catarrhal jaundice or that due to stone in the common bile duct. Mateer and Hartman [18] found this method of determining whether bile is entering the duodenum to be such a reliable index of malignant obstruction, arising from the head of the pancreas, the common bile duct or the ampulla or papilla of Vater, that they have formulated the following rule: "If three attempts are made to obtain

18. Mateer, John G., and Hartman, F. W.: Primary Carcinoma of the Duodenum, J. A. M. A. **99**:1853 (Nov. 26) 1932.

bile from the duodenum during the course of a week or ten days of study, and no bile is obtained on any of these occasions, one can be reasonably certain that the jaundice is due to malignant obstruction of the lower biliary tract." The van den Bergh test and determination of the icteric index furnish information of value and should be employed in all cases in which biliary obstruction is present or is suspected.

Examination of the stools will reveal evidence of obstruction of the bile or pancreatic duct by changes in the character and appearance of the stools. Depending on the degree and rate of the loss of blood, the stools will be tarry or show evidence of occult blood.

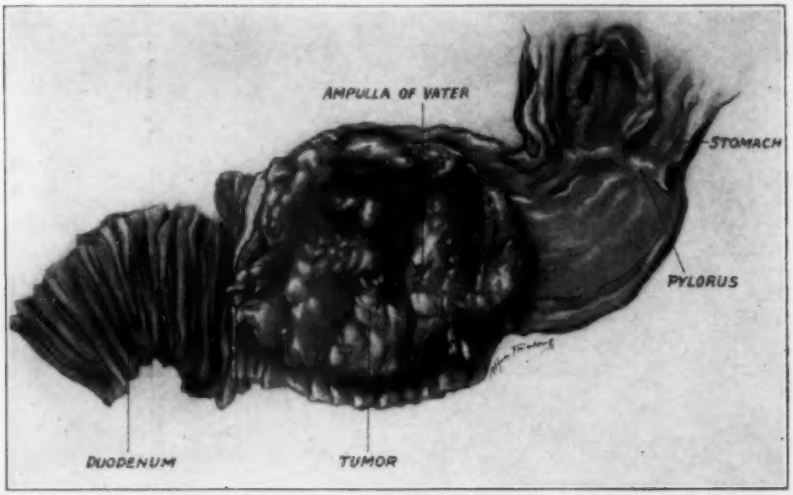


Fig. 10 (case 3).—Artist's drawing of the gross specimen of a carcinoma of the periampullary portion of the duodenum found at autopsy.

The urine is usually concentrated, with a high specific gravity. If biliary obstruction is present, bile will be evident; if the pancreas is damaged, there may be glycosuria.

CLINICAL COURSE

Cancer of the duodenum, as a rule, follows a steady progressive course. The onset is insidious, with vague epigastric pain and moderate gastric disturbance, until obstruction of the duodenum or bile passages ushers in a rapidly developing train of symptoms of obstruction. This is associated with a swift decline in the patient's strength and general condition, as the functions of nutrition, hydration and excretion become increasingly difficult. The only remissions are those which occur when obstructing tumors undergo necrosis and slough, permitting a temporary release of the obstruction. The disease is rapidly fatal, and the average

duration of life is about seven months after the onset of the first symptoms. The shortest duration of life is found with lesions around the ampulla, and the longest duration, with those involving the first portion. The shortest duration in our series was six weeks from the onset of the symptoms to death (case 6); the longest duration (case 17) was two years.

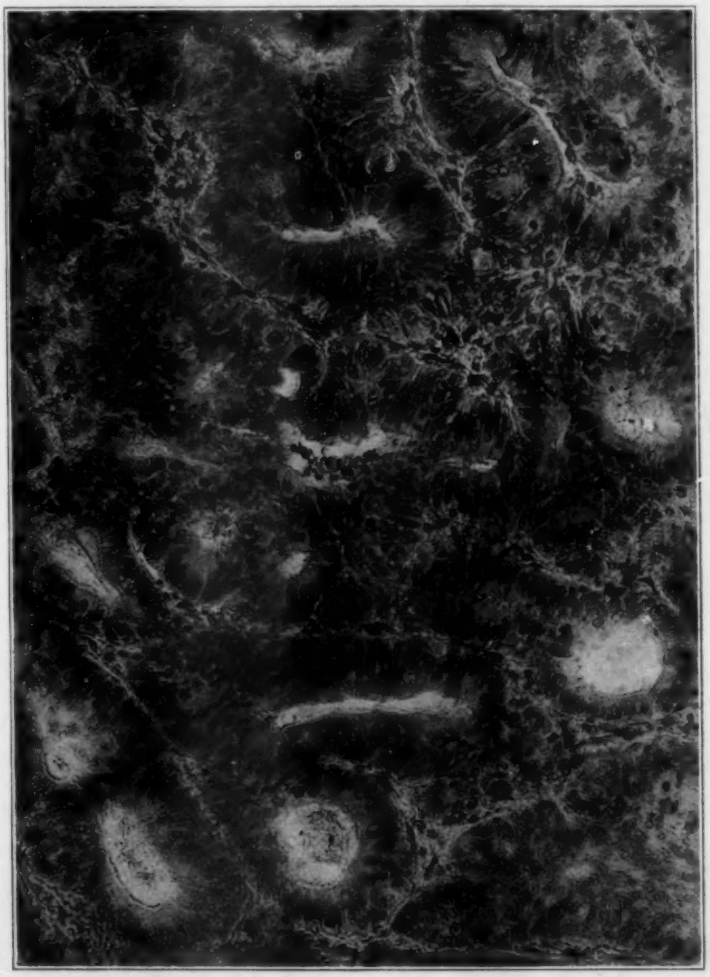


Fig. 11 (case 3).—Microscopic section of the carcinoma of the periampullary portion of the duodenum demonstrated in figure 9. The growth was a malignant adenoma.

ROENTGENOGRAPHIC AND FLUOROSCOPIC FINDINGS

Roentgenographic examination in an early stage of cancer of the duodenum may fail to disclose anything abnormal despite the most

careful scrutiny. A moderately advanced lesion, however, may yield evidence of involvement. When the tumor is located in the supra-ampullary portion, there may be narrowing and irregularity of the outline of the base of the bulb or deformity of the margin of the duodenal cap, as shown in figure 6. Findings like these, however, in the absence

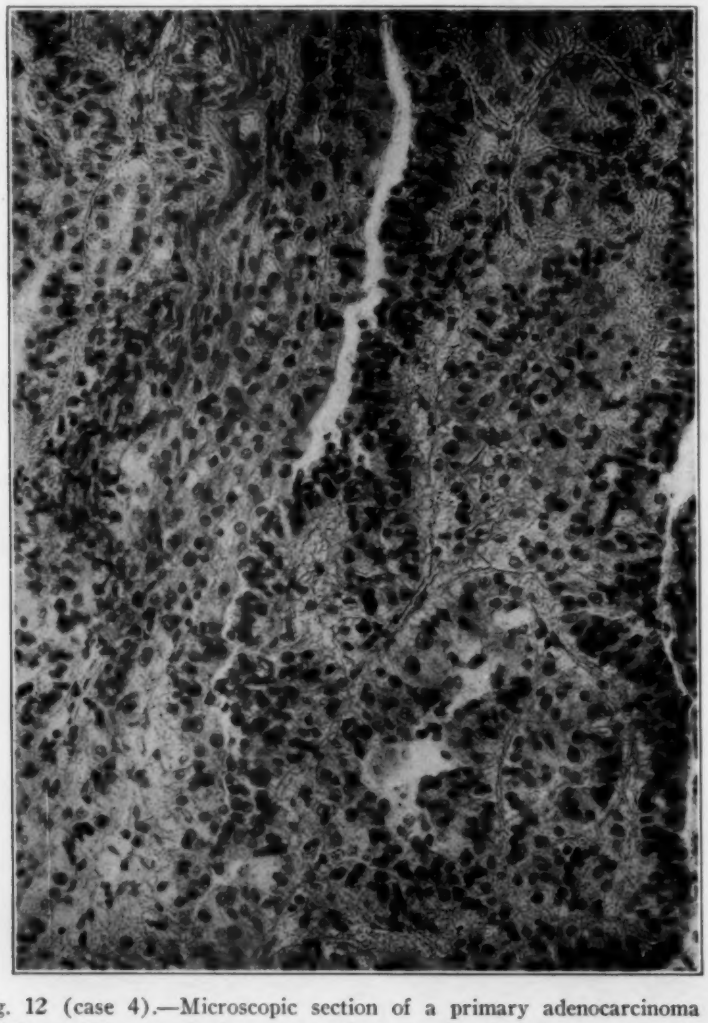


Fig. 12 (case 4).—Microscopic section of a primary adenocarcinoma of the right kidney. Five months later the patient was found to have a second primary malignant tumor—a carcinoma of the periampullary portion of the duodenum.

of any marked symptoms, are usually interpreted as deformities and contractures due to chronic duodenal ulcer. As soon as the neoplastic process has caused partial obstruction of the duodenal lumen, the stomach makes vigorous efforts to expel its contents through the duo-

denum, and the increased peristaltic efforts are evident on the screen and films. After the obstruction is well established, the gastric musculature becomes exhausted and the organ becomes distended. The gastric shadow, greatly enlarged, shows diminished motility and evidence of retention of 30 per cent or more of the barium sulfate after six hours. At this stage the pylorus becomes widely dilated, so that it may be difficult to define it. The annular carcinomatous constriction in the first portion of the duodenum may be interpreted as a normal pylorus, while the dilated pylorus itself may be mistaken for the gastric antrum (case 4). The duodenal cap is structurally the weakest part of the duodenum, and at an early stage of the disease it may appear on the screen

Fig. 13 (case 4).—Roentgenogram showing a large duodenal cap and irregularity of outline of the second portion of the duodenum. Autopsy revealed a primary carcinoma of the periampullary portion of the duodenum (fig. 10).

or film as a greatly dilated organ outlined with striking clarity. This appearance may be the only evidence of a beginning slight obstruction. One of our patients showed this phenomenon four months before there were any severe symptoms or other roentgenographic evidence of obstruction (case 4, fig. 13).

When the obstruction is in the periampullary portion of the duodenum, the roentgenographic features include marked peristalsis, retention of barium, distention of the pylorus and duodenal cap and an irregular outline of the lower limit of the column of barium at the point of obstruction (figs. 13 and 19). Above this level, the distended duodenum may be visualized with unusual distinctness. If the obstruc-

tion is well marked, movements of reverse peristalsis may be observed on the fluoroscopic screen. The gaping pylorus may be demonstrated fluoroscopically, and light manual pressure over the duodenum may be

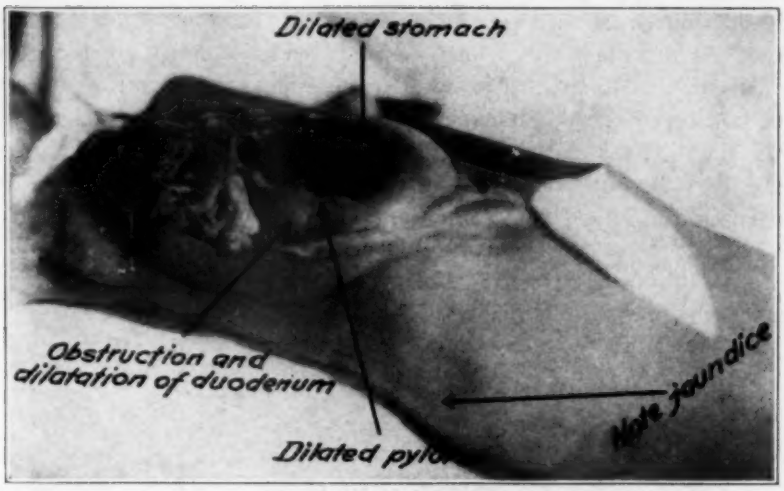


Fig. 14 (case 4).—Photograph of the specimen obtained at autopsy. Note the greatly distended stomach, dilated pylorus, distended duodenal cap and sharply demarcated obstruction around the ampulla of Vater. The color of the skin was due to intense jaundice.

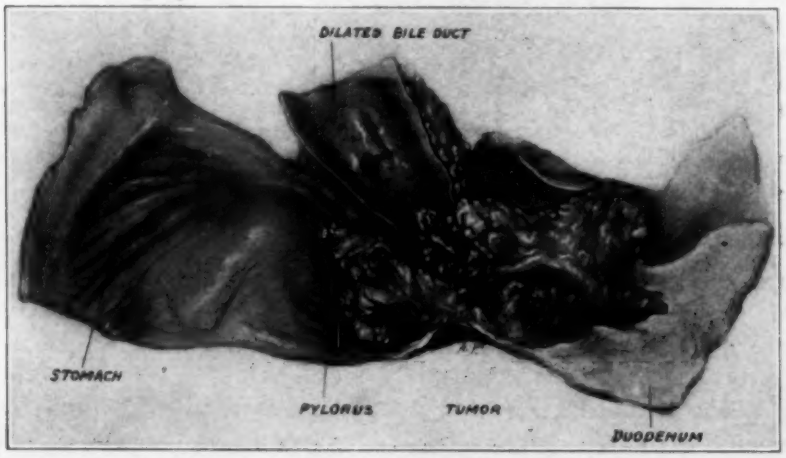


Fig. 15 (case 4).—Artist's drawing of the gross specimen found at autopsy. Note the greatly dilated bile duct and carcinoma surrounding the ampulla of Vater.

sufficient to force the duodenal contents backward into the stomach without the pylorus apparently interposing any obstacle.

Cancer of the infra-ampullary portion of the duodenum often is a long bulky lesion involving a considerable portion of the duodenum (figs. 7, 17 and 26). Roentgenographically, this lesion is featured by irregularity of a large portion of the duodenum. Sometimes a distinct

Fig. 16 (case 4).—Microscopic section of the growth demonstrated in figure 13, showing malignant adenoma.

canalization of an extensive tumor is seen. At a later stage, when the obstruction has become more nearly complete, the entire duodenum above the obstruction may be clearly outlined as a dilated C-shaped tube (fig. 7). When the obstruction is below the ampulla of Vater, the

accumulated bile and pancreatic juice above the lesion occasionally produce a definite fluid level, above which is sometimes seen a large air bubble (Kummer [19]). Cancer of the third portion of the duodenum, because of its bulk and tendency to invade the pancreas, may cause the duodenal loop to curve around in a wide circle, imitating the appearance occasionally produced by a bulky carcinoma of the head of the pancreas, with which cancer of the second or third portion of the duodenum frequently is confused. This finding was present in 2 of our cases (nos. 3, and 11, fig. 9).

When cancer of the duodenum produces biliary obstruction (cancer of the periampullary or infra-ampullary portion), the gallbladder usually

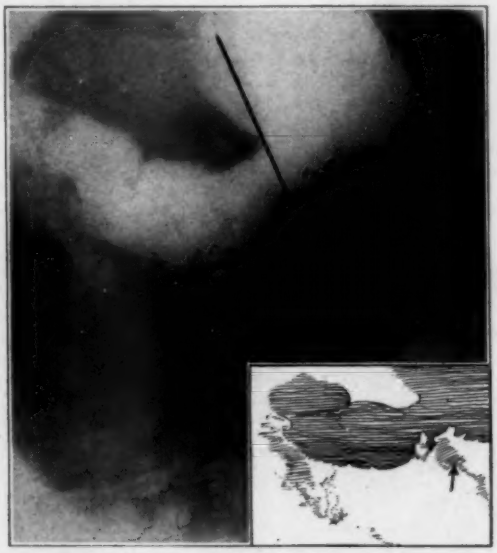


Fig. 17 (case 7).—Terminal portion of the duodenum involved by a tumor, causing deformity of outline and partial obstruction.

is dilated, in accordance with Courvoisier's law. The organ, however, is not always palpable because of the enlarged, overhanging liver. Demonstration of its enlargement and its failure to empty normally can be made by cholecystography and thus furnish evidence that the obstruction is caused by a malignant tumor rather than by an impacted stone.

Other conditions to be differentiated from carcinoma of the duodenum include benign tumor, contraction due to scarring of chronic ulceration, diverticulum and pressure due to external masses. The

19. Kummer, E.: Occlusion chronique de l'angle duodéno-jéjunal, Bull. et mém. Soc. de chir. de Paris **46**:1161, 1920.

benign tumors are exceptionally rare. Ross Golden [20] summarized 17 cases from the literature and added 2 of his own. The tumors included adenoma, myoma, fibro-adenoma, hemangioma and lymphangio-endothelioma. Many of these lesions are pedunculated. Roentgen examination shows a central radiolucent filling defect which may be circular,

Fig. 18 (case 8).—Microscopic section of a carcinoma of the periampullary portion of the duodenum, showing malignant adenoma and adenocarcinoma.

vacuolar or multilocular, lying within and surrounded by the barium shadow of the duodenal bulb. A sessile tumor arising in the stomach

20. Golden, Ross: Non-Malignant Tumors of the Duodenum, Am. J. Roentgenol. **20**:405 (Nov.) 1928.

may prolapse through the pylorus into the duodenum and produce a similar defect in the barium shadow (fig. 2). Eliason, Pendergrass and Wright [21] have shown that when prolapsing gastric mucosa is accompanied by a prolapsing polyp or new growth two filling defects are produced, one in the bulb by the pedunculated tumor and another in the pylorus by the hypertrophied gastric mucosa. In these cases an important diagnostic point is the absence of the filling defect in a roentgenogram made with the patient in the erect position and the presence of the defect in one made with the patient in the prone position.

In differentiating a benign tumor from an ulcer, it should be remembered that an ulcer does not produce a central filling defect. The niche

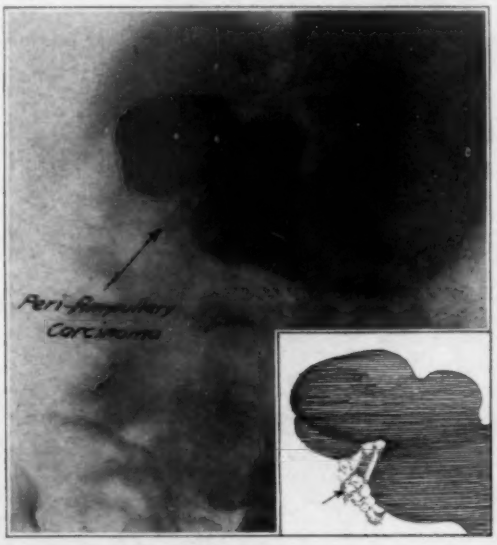


Fig. 19 (case 10).—Carcinoma of the periampullary portion of the duodenum. The stomach was not dilated, and there was active peristalsis. The first portion of the duodenum was obscured by the antrum of the stomach. There were irregularity, narrowing and deformity of the descending portion of the duodenum.

produces a constant disturbance in the outline of the bulb and may be associated with an incisura. The usual finding is hyperperistalsis with delay in motility. Adhesions usually produce an irregularity of the outline of the bulb, with fixation, gastric hyperperistalsis and delayed motility.

A tumor in the region of the pancreas, pressing on the barium-filled lumen, may produce a central translucency of intraluminal growths,

21. Eliason, E. L.; Pendergrass, E. P., and Wright, V. W. M.: Roentgen Ray Diagnosis of Pedunculated Growths and Gastric Mucosa Prolapsing Through the Pylorus, Am. J. Roentgenol. **15**:295, 1926.

but it is exceptional to have the defect confined to the cap and remain constant in all the horizontal positions (Shiflett [22]).

Diverticulum of the duodenum is not an exceptionally rare finding. Ritchie and McWhorter [23] collected reports of 76 cases from the literature, and Morrison and Feldman [24] reported 12 personal cases, in 1 of which a carcinoma developed. The best method of recognizing a diverticulum is fluoroscopy, during which the examiner can, by manipulation, cause the pouch to fill and empty. The appearance is characteristic, with regular and smooth outlines. When the ostium of the diverticulum

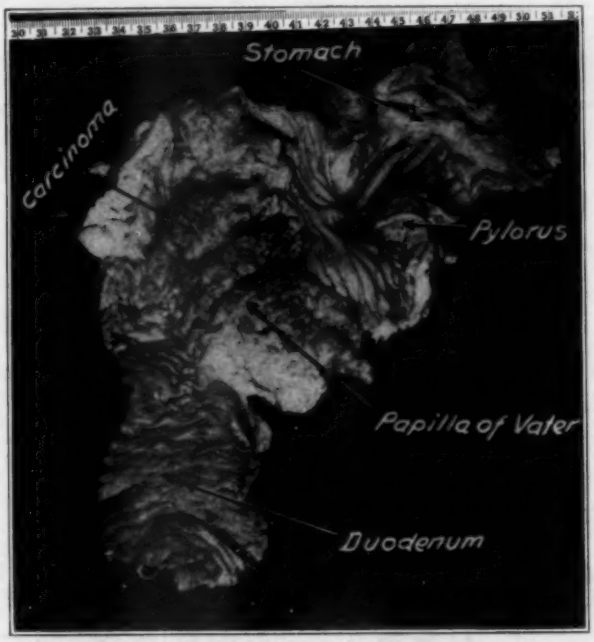


Fig. 20 (case 10).—Photograph of the gross specimen of a carcinoma of the periampullary portion of the duodenum demonstrated in figure 19.

is small, the barium may be retained in a diverticulum for as long as fifty-two days (LeWald [25]). The importance of diverticulum in con-

22. Shiflett, E. L.: Tumors of the Duodenum and Hypertrophied Gastric Mucosa Prolapsing Through the Pyloric Canal into the Duodenum, Radiology **19**:79, 1932.

23. Ritchie, H. P., and McWhorter, G. L.: Duodenal Diverticula, Surg., Gynec. & Obst. **25**:485, 1917.

24. Morrison, T. H., and Feldman, M.: A Case of Carcinoma in a Duodenal Diverticulum with a Consideration of Duodenal Diverticulosis, Ann. Clin. Med. **4**:403 (Nov.) 1925; Autopsy Report of a Case of Primary Carcinoma in a Duodenal Diverticulum, ibid. **5**:326, 1926.

25. LeWald, L. T.: Right-Sided Diverticulitis and Diverticulosis, Radiology **4**:1 (Jan.) 1925.

nection with carcinoma of the duodenum is twofold: First, carcinoma may arise in a diverticulum (Morrison and Feldman [24]) and, second, the crater of an ulcerated carcinoma may duplicate the roentgenographic appearance of a diverticulum, as occurred in case 12 of our series (figs. 21, 22 and 23).

The difficulties encountered and the errors made in the roentgen examination in cases of cancer of the duodenum are illustrated by the record of this series. Of the 18 cases reported here, roentgenograms of the gastro-intestinal tract were made in 16. The results are shown in table 2. From a study of this it is seen that in the 3 cases in which the lesion was located above the ampulla definite abnormalities were

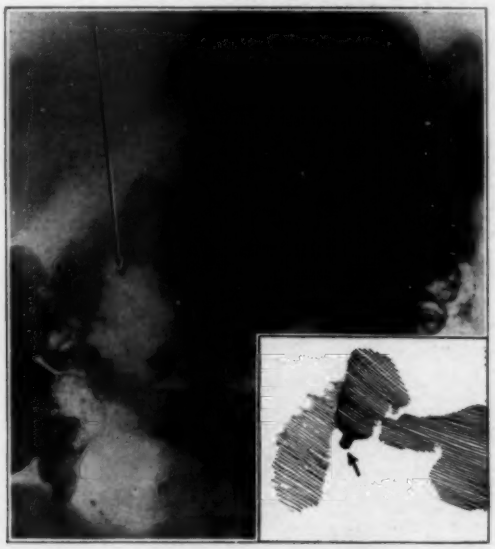


Fig. 21 (case 12).—Carcinoma of the periampullary portion of the duodenum simulating a diverticulum. Note the prominent duodenal bulb and what appears to be a diverticulum of the first portion of the duodenum. At operation this proved to be the crater in an ulcerated carcinoma of the periampullary portion of the duodenum.

noted. The diagnosis of a malignant growth was made in 1 case and suggested as a possibility in another. In only 1 case was a malignant tumor of the duodenum suspected. The diagnoses were "carcinoma of the pylorus," "obstruction of the duodenum, possibly malignant," and "pyloric obstruction." In 7 of the 9 cases of carcinoma in the periampullary portion of the duodenum, roentgenographic studies of the gastro-intestinal tract were made. The diagnoses were, respectively, "carcinoma of the head of the pancreas," "negative" (2 cases), "per-

forating ulcer," "diverticulum," "obstruction of the second portion of the duodenum" and "biliary obstruction with deformity of duodenum, probably from adhesions." In 6 cases of carcinoma of the infra-ampullary portion the diagnosis was, respectively, "carcinoma of the head of the pancreas," "negative," "duodenal obstruction, probably due to adhesions, but pancreas may be involved" and "deformity and narrowing of duodenum" and (in the 2 remaining cases) "duodenal obstruction."

Here, then, are the diagnoses, made by 6 roentgenologists based on the roentgen examinations in 16 cases in which clinical symptoms were

Fig. 22 (case 12).—Roentgenogram of the carcinoma demonstrated in figure 21. Note the barium retained in the crater of the ulcerated carcinoma.

present. In all but 1 of them obvious pathologic changes were evident on the films, yet in only 1 instance was the possibility of a primary carcinoma of the duodenum suggested. In 14 instances, however, the abnormal findings were recognized and described. The conclusions which seem to be justified are: The diagnosis of carcinoma of the duodenum occasionally will be made from the roentgen picture alone, but in most cases a careful correlation and synthesis of the evidence and information derived from all possible methods of clinical investigation are necessary.

Fig. 23 (case 12).—Roentgenogram of the carcinoma demonstrated in figure 21. Note the barium retained in the crater for twenty-four hours.

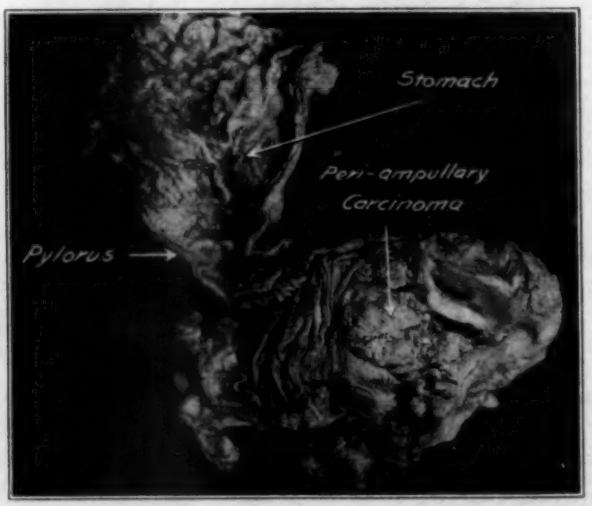


Fig. 24 (case 12).—Gross specimen of the carcinoma shown in figure 21.

DIAGNOSIS

The diagnosis of cancer of the duodenum is attended with so much difficulty that most of the recorded cases were recognized only at operation or at autopsy. In only a few cases reported in the literature

TABLE 2.—*Summary of Roentgen Findings and Diagnosis*

Patient	Location of Growth	Roentgen Findings	Roentgen Diagnosis
M. B.	Supra-ampullary	Dilated pylorus; deformed duodenum distal to cap	Carcinoma of pylorus
D. H.	Infra-ampullary	Deformity of duodenal cap; widening of duodenal loop	Carcinoma of head of pancreas
B. K.	Periampullary	Infiltration of duodenum; gastric retention; enlarged gallbladder	Carcinoma of head of pancreas
C. S.	Periampullary	Hypomotility; large duodenal cap; irregular outline of second portion, partial obstruction of duodenum	No pathologic process
H. S.	Supra-ampullary	Filling defect in junction of first and second portions of duodenum with obstruction and retention	Inclined to think growth benign but must consider possibility of malignancy
L. H.	Supra-ampullary	Almost complete "pyloric obstruction with retention of 90% of barium at 6 hr."	Pyloric obstruction
M. B.	Infra-ampullary	No evidence of cancer or ulcer; no obstruction or dilatation	No evidence of cancer or ulcer in either stomach or duodenal cap; no obstruction or dilatation
H. B.	Infra-ampullary	Obstruction of second and fourth portions of duodenum with gastric retention	Obstruction, probably due to adhesions, but pancreas may be involved
A. B.	Intra-ampullary	Stomach not dilated; active peristalsis; first portion of duodenum obscured by antrum of stomach; irregularity, deformity and narrowing of descending portion of duodenum	No definite diagnosis made
S. A.	Periampullary	Duodenal outline irregular and curves far out to right; 6 hr. retention in stomach; ulcer crater in second portion of duodenum; gallbladder enlarged	Perforating ulcer
J. R.	Infra-ampullary	Obstruction of third portion of duodenum; marked dilatation of entire duodenum and retention of barium	Obstruction of duodenum
W. F.	Infra-ampullary	Obstruction of third portion of duodenum; moderate retention of barium in terminal portion of duodenum; no dilatatoin	No diagnosis made
F. K.	Periampullary	No roentgenograms of gastro-intestinal tract made; injection of biliary tract through gallbladder drain showed dilatation of biliary duct system and obstruction of common duct at ampulla	Dilatation of bile duct
A. B.	Periampullary	Distended gallbladder; irregularity and deformity of second portion of duodenum; no gastric retention	Biliary obstruction; deformity of duodenum probably the result of adhesions
G. B.	Periampullary	Obstruction of second portion of duodenum	Obstruction of second portion of duodenum
C. G.	Periampullary	No evidence of pathologic process in stomach or duodenum (studies made twelve months before admission to hospital)	No evidence of pathologic process in stomach or duodenum

has the condition even been suspected. Because of its rarity, it is usually not even considered as a possibility in the differential diagnosis. A further explanation is the fact that cancer of the duodenum is usually mistaken for other lesions of the upper portion of the abdomen. Nevertheless, if the possibility of carcinoma of the duodenum is given

consideration, it should be feasible to make a presumptive diagnosis in certain of these cases. In the early stage, however, symptoms are so few that such a hope is probably not justified, and the diagnosis must await exploratory operation.

The presenting symptoms of cancer of the duodenum usually are epigastric pain and obstruction of the upper part of the intestinal tract,

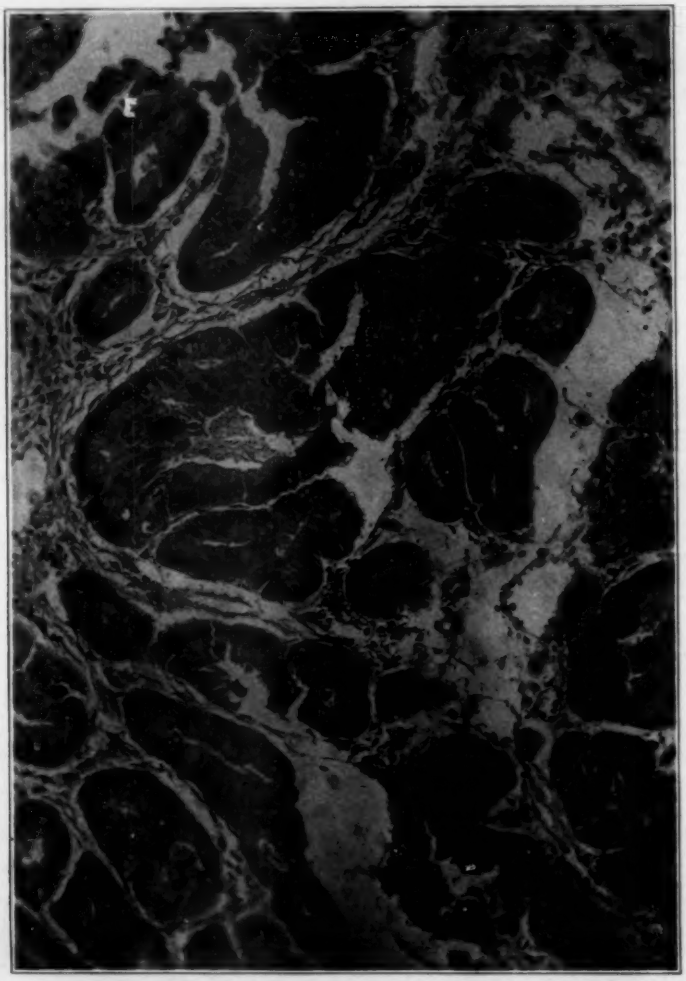


Fig. 25 (case 12).—Microscopic section of the adenocarcinoma shown in figure 21.

with or without biliary obstruction and jaundice. The logical sequence of procedure, naturally, is to locate the level of the obstruction definitely and finally to determine its cause. The indication that the level of the obstruction is in the stomach, duodenum or upper part of the jejunum

is furnished by the presence of gastric retention and dilatation, the absence of intestinal contents in the vomitus and the flat or sunken abdomen without gaseous distention. The commonest obstructive lesion in this region is a carcinoma of the pylorus. This can be ruled out by the roentgen examination revealing a normal gastric outline and motility and a patent or even dilated pylorus. Should the gastric analysis disclose normal free hydrochloric acid, it will help exclude the stomach as the primary site; if diminished or absent, it will not be conclusive.

If bile and pancreatic juice are not found in the vomitus and there is no evidence of jaundice, the point of the obstruction will be in the supra-ampullary portion of the duodenum. The presence of biliary obstruction and jaundice definitely locates the obstruction in the neighborhood of the ampulla, and roentgenograms may show a dilated first portion of the duodenum above an irregular constriction, a gaping

Fig. 26 (case 13).—Obstruction of the third portion of the duodenum with dilatation and retention of barium in the stomach and duodenum after six hours.

pylorus, distended stomach and retention of barium after six hours (figs. 19 and 27). Obstruction of the jejunum can be ruled out by the absence of intestinal contents in the vomitus and by roentgen studies. If the roentgenogram reveals a long, dilated proximal portion of the duodenum above a point of obstruction, with or without irregularity of the duodenal lumen, it is fair to assume that the lesion is in the third portion of the duodenum (fig. 26). When the lesion is below the ampulla of Vater, bile and pancreatic juice are usually found in the gastric contents on repeated examinations, as Mateer and Hartman [18] and others have emphasized.

Even after the level of obstruction has been determined or assumed, a definite diagnosis of cancer of the duodenum cannot be made until other nonmalignant causes of obstruction have been eliminated. The commonest cause of obstruction of the first portion of the duodenum

is constriction by scars of a chronic duodenal ulcer. Evidence against such a cause and in favor of a malignant growth would be the lack of any characteristic history of ulcer, the more rapid development of emaciation, cachexia and stenosis, a marked decrease or absence of free hydrochloric acid, the presence of a palpable tumor and the failure to demonstrate an ulcer by roentgen examination (Eger [16]).

Of all causes of obstruction of the supra-ampullary portion of the duodenum by external pressure mentioned by various authors, enlargement of the gallbladder is, perhaps, the most frequent. Others are: tumors of the omentum, kidney, pancreas and liver, enlarged retroperitoneal glands and an aneurysm of the celiac axis or of the hepatic

Fig. 27 (case 16).—Carcinoma of the periampullary portion of the duodenum. Note the irregularity and deformity of the second portion of the duodenum.

artery (Fenwick [26]). In differentiating these from cancer of the duodenum, the greatest weight must be given to the following findings, which are common in association with cancer of the duodenum and rare with these other conditions: a severe degree of obstruction of short duration and rapid development, marked cachexia and loss of weight, the presence of blood in the vomitus and stools and marked decrease or absence of free hydrochloric acid in the gastric secretion. Additional aid may be afforded by roentgenographic study of the gallbladder, although it must be remembered that this organ is usually enlarged

26. Fenwick, W. S.: Primary Carcinoma of the Duodenum, Edinburgh M. J. **10**:309, 1901.

whenever biliary obstruction is produced by a malignant tumor, whether the primary site is the common duct, ampulla, papilla, head of the pancreas or duodenum.

Cancer of the periampullary portion of the duodenum, therefore, is even more difficult to differentiate from obstruction due to other causes. Acute pancreatitis usually has an explosively swift onset, with violent pain and without actual obstruction of the duodenum or alteration in the quantity of free hydrochloric acid in the gastric secretions. Chronic pancreatitis and carcinoma of the head of the pancreas are not likely to cause obstruction of the duodenum or produce blood in the stools or vomitus or cause any reduction in free hydrochloric acid. Cancer of the bile duct, ampulla or papilla causes jaundice of a rapidly progressive unremitting, obstructive type, without symptoms or signs by which it can be differentiated prior to operation or autopsy.

Cancer of the infra-ampullary portion of the duodenum is usually an extensive tumor, often bulky and frequently located immediately proximal to the ligament of Treitz (fig. 26). It, therefore, often may furnish adequate roentgen signs by which the location and extent of the involvement may be fairly well indicated. The differentiation of an obstruction at this level from one in the supra-ampullary portion may be aided by the consistent finding of bile and pancreatic juice in the gastric contents. Other causes of obstruction in the infra-ampullary portion, such as enlargement of the retroperitoneal nodes, retroperitoneal tumor, pressure by superior mesenteric vessels, impaction of a large gallstone in the duodenum and external pressure from a tumor of a contiguous viscus such as the pancreas, must be considered (Eger [16]).

The difficulty of diagnosing cancer of the duodenum is illustrated by the records of this series of 18 cases. Although we have personally examined and studied 5 patients, in only 1 instance was the suggestion made that the lesion might be a primary carcinoma of the duodenum.

TREATMENT

Study of any large series of cases of duodenal carcinoma will reveal two outstanding facts: (1) In a large percentage of cases no evidence of metastasis or local extension of the disease is found at operation, and (2) a high mortality accompanies operative attempts at cure. The first point suggests that successful surgical removal of all the malignant disease might often be feasible if this mortality could be brought down to a reasonable level. The reason for the high mortality is obvious. Not only are the surgical procedures of unusual magnitude, but they must be carried out on patients who often are already moribund from the effects of interference with vital processes. Most of these patients have symptoms of high intestinal obstruction, often complicated by

TABLE 3.—*Summary of Diagnostic Data of Primary Ca*

	Origin in Duodenum*	Sex	Age, Years	Duration of Symptoms	Pain in Right Upper Quadrant and Epigastric Distress	Vomiting	Jaundice	Fever and Evidence of Sepsis	Loss of Weight	Palpable Mass in Epigastrium	Palpable Edge of Liver	Occult Blood in Stools	Bile in Stools	Bile in Urine	Biliary Drainage, Bile Obtained
Case 1.....	Supra	F.	48	4 mo.	Yes	No	No	No	Yes	Yes, 5 cm., movable	No	No	Yes	No	—
Case 2.....	Infra	F.	28	6 mo.	Yes	Yes	No	No	Yes	Yes, 12 cm., fixed	No	—†	—	No	—
Case 3.....	Peri	F.	60	3 mo.	Yes	No	No	No	Yes; emaciated	Yes, 10 cm., movable	No	—	—	No	—
Case 4.....	Peri	F.	47	2 mo.	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No; clay colored	Yes	—
Case 5.....	Supra	F.	68	9 mo.	Yes	Yes	No	No	Yes; 20 lb.	Yes	Yes	No	Yes	—	—
Case 6.....	Supra	F.	70	5 wk.	Yes	Yes	No	Yes	Yes; emaciated	No	No	No	Yes	—	—
Case 7.....	Infra	F.	51	10 mo.	Yes	Yes	Yes	No	Yes; 40 lb.	No	No	..	..	Yes	—
Case 8.....	Peri	F.	52	6 wk.	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	—
Case 9.....	Infra	M.	78	6 mo.	Yes	Yes	No	No	Yes; 25 lb. in 6 wk.	Yes	No	—	—	No	—
Case 10.....	Infra	M.	71	1 yr.	No	No	No	No	No	No	No	No	No	No	—
Case 11.....	Peri	M.	18	1 yr.	Yes	No	Yes	No	Yes	Yes; 8 cm. in diameter; moderately movable	No	—	No	No	—
Case 12.....	Peri	F.	56	2 mo.	Yes	No	Yes	Yes	Yes	Yes; definite mass	No	No	No; pale	No	—
Case 13.....	Infra	M.	51	2 yr.; gastric distress	Yes	Yes	No	No	30 lb. in 6 wk.	No	...	..	..	...	..
Case 14.....	Infra	M.	?	.....	Yes	...	No	No	Yes	Yes	...	..	..	...	..
Case 15.....	Peri	F.	36	2 mo.	Yes	Yes	Yes	Yes	Yes; extreme loss	No	Yes	No	No	Yes	..
Case 16.....	Peri	M.	58	6 wk.	Yes	No	Yes	Yes	Yes	No	No	No	No; pale	Yes	—
Case 17.....	Peri	F.	45	6 wk.	Yes	Yes	No	No	Yes	Yes	No	No	Yes	No	—
Case 18.....	Peri	F.	45	1 yr.	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Sligh amou of bil obtain

* Supra refe peri-ampullary
† The dash

Bile in Stools	Bile in Urine	Biliary Drainage, Bile Obtained	Icteric Index	Gastric Analysis	Roentgen Picture with Barium Meal	Course
Yes	No	—	—	Normal	Dilated pylorus; deformed duodenum distal to cap	Died 8 days after gastroenterostomy of acute surgical parotitis (bilateral)
—	No	—	—	—	Deformity of duodenal cap; widened loop	Exploratory laparotomy showed mass thought to be retroperitoneal sarcoma; after 12 roentgen treatments mass regressed; after 6 mo. recurred; radium pack treatments ineffectual; laparotomy and implantation of radon seeds; died 4 days later
—	No	—	—	—	Pressure defect of greater curvature of stomach; infiltration of duodenum; gastric retention after 6 hours; enlarged liver shadow	Exploratory laparotomy; death from peritonitis
No; clay colored	Yes	—	—	—	Dilated first portion of duodenum with irregular outline of second portion and partial obstruction	Rapid downhill course, patient vomiting large amounts of bile-stained fluid; death 33 days later
Yes	—	—	—	—	Persistent filling defect of junction of first and second portions of duodenum with obstruction and 48 hours gastric retention	Posterior gastro-enterostomy for cancer of duodenum causing obstruction, involving the first and second parts of duodenum; tumor hard and elastic and obviously malignant; no metastases; no biopsy
Yes	—	—	—	—	Almost complete pyloric obstruction with 90% retention at 6 hours	Death 3 days after admission due to myocardial failure
..	Yes	—	Increased	—	Involvement of duodenojejunal junction by irregular mass causing partial obstruction	Rapid downhill course; stercoraceous vomiting and death in 3 days
No	Yes	—	Increased	—	.....	Rapid decline; death week after admission
—	No	—	Normal	—	Obstruction of second and fourth portions of duodenum with gastric retention	Anterior gastro-enterostomy and entero-enterostomy; death 8 days later due to peritonitis
No	No	—	Normal	—	Dilatation of duodenal cap and first portion; second portion irregularly narrowed and deformed; no diagnosis made	Steady downhill course; death 3 months later
No	No	—	Increased	Normal	Duodenal outline irregular and curves far out to right; 6 hour retention in stomach; ulcer crater in lower part of second portion of duodenum; gallbladder shadow enlarged	Untraced
No; pale	No	—	35	—	Shadow of duodenal cap large; second portion narrowed; barium retained in crater in second portion after 24 hours; considered to be diverticulum	Exploratory laparotomy; tumor of second portion of duodenum found and exposed by duodenostomy; distended gallbladder drained by cholecystostomy; death 7 days later due to bronchopneumonia
..	...	..	..	..	Obstruction of terminal portion of duodenum; dilatation of duodenum; 6 hour retention of barium	Lived 2 years
..	...	..	..	..	Obstruction of terminal portion of duodenum; small retention; no dilatation	Untraced
No	Yes	..	100	..	No gastric studies made; dilated bile ducts shown by injection through gallbladder drainage tube	Downhill course; death 4 months after admission
No; pale	Yes	—	?	—	Irregularity and deformity of second portion of duodenum; gallbladder distended	Exploratory operation; obstruction of common duct; no stone found; T tube inserted; biliary obstruction relieved; hemorrhage from wound 4 weeks later; duodenum exposed and carcinoma excised; death 6 hours later
Yes	No	—	—	—	Obstruction of second portion of duodenum with marked dilatation of duodenum and gastric residue	Posterior gastro-enterostomy and cholecystogastrostomy; recovery; lived 2 years
No	Yes	Slight amount of bile obtained	133	Normal	Negative (12 months before admission)	Steady downhill course for 1 year terminated by massive hemorrhage from duodenal tumor

* Supra refers to the supra-ampullary portion of the duodenum; infra, to the infra-ampullary portion, and peri, to the peri-ampullary portion.

† The dash indicates that this part of the examination was omitted in this case.

biliary obstruction and chronic hemorrhage. They commonly show advanced degrees of starvation, dehydration, acidosis, anemia, jaundice and gastric distention. A high mortality cannot be avoided if such patients are operated on without adequate preparation.

The dehydration should be corrected by the daily administration of from 3,000 to 5,000 cc. of fluids by all routes. At least from 1,000 to 2,000 cc. of 1 per cent solution of sodium chloride and 10 per cent dextrose should be given intravenously daily. The stomach should be washed out at least once a day. Studies of the blood chemistry will indicate the progress of the patient. The anemia must be corrected by frequent transfusions, preferably of whole blood, which provides ideal nourishment and stimulation to these prostrated patients.

With jaundice present, the danger of hemorrhage increases. Even though jaundice may not be clinically evident, the amount of circulating bilirubin may, nevertheless, increase 800 to 1,000 per cent. The van den Bergh test, determination of the icteric index and estimation of the bleeding and the coagulation time furnish important information. Patients with jaundice should be prepared for operation by restoring the supply of calcium, sodium chloride, water and especially carbohydrates. Walters [27] recommended the administration of 5 cc. of a 10 per cent solution of calcium chloride intravenously for three days; 100 grains (6.5 Gm.) of calcium lactate by mouth daily for four days, and 4,000 cc. of water by all available avenues. In addition, proctoclysis of from 3 to 15 per cent dextrose solution is suggested. A 10 per cent solution of dextrose intravenously is the most direct way of supplying the carbohydrate which is almost a specific for hepatic insufficiency. With such a preparatory regimen, including blood transfusions, Walters [27] was able to reduce the coagulation time from fourteen to two minutes.

OPERATIVE PROCEDURES

The surgical procedures for the treatment of cancer of the duodenum are of two general classes: curative and palliative. In the first group the procedure must be varied according to the location and extent of the growth and the complications which accompany it. Rarely the primary growth may be so small that a simple excision may be sufficient (fig. 3). In the usual case, however, the growth involves so much of the lumen of the duodenum that a resection of the whole segment must be done. If the tumor is in the supra-ampullary portion, well above the bile and pancreatic ducts, this procedure plus posterior gastroenterostomy should be sufficient (fig. 4).

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27. Walters, Waltman: Obstructive Jaundice: Its Surgical Aspects, Ann. Surg. **93**:1137 (April) 1931.

Carcinoma of the periampullary portion, accompanied by biliary obstruction, entails radical excision of the affected segment, and, if possible, reimplantation of the common bile duct and the duct of Wirsung into the duodenum (fig. 5). When this is done, Cohen and Colp [8] recommended that some operation be done to provide drainage of the gallbladder and thus take the strain off the newly implanted bile duct. The operations which may be employed are choledochostomy, cholecystostomy and cholecystenterostomy. Despite the fact that the addition of this procedure increases the mortality slightly, its advantages deserve consideration. Tension is certainly taken off the suture line, the flow of bile is assured, and should stricture or local recurrence develop, as happened in the cases of Mayo [28] and Rixford,[29] a second operation would not be necessary (Cohen and Colp [8]).

If simple excision of the tumor of the periampullary region (fig. 3) is not sufficiently radical to get beyond the growth, it may be necessary to perform a circular resection of the duodenum, combined with partial pancreatectomy (fig. 4). Cohen and Colp reviewed the literature up to 1927 and found only 4 instances in which the patients had survived this formidable procedure. These were the celebrated cases of Halsted,[28] Kausch,[30] Hirschel [31] and Tenani.[32]

Halsted in 1898 resected a portion of the duodenum, restored its continuity by an end to end anastomosis, reimplanted the bile and pancreatic ducts and established a cholecystostomy stoma. Three months later cholecystoduodenostomy was performed. Kausch did a preliminary cholecystojejunostomy, and two months later resected the duodenum and part of the pancreas and performed pancreaticoduodenostomy and gastro-enterostomy. Tenani, more recently, at his first operation, did an exploratory duodenotomy, followed by posterior gastro-enterostomy, and after dividing the bile duct, he implanted the proximal end into the efferent duodenal segment. He then sutured the duodenum and closed the abdomen without drainage. One month later he resected the second portion of the duodenum and the involved portion of the head of the pancreas. The pancreatic stump was sutured into the efferent duodenal segment (fig. 3).

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28. Cited by Upcott, H.: Tumors of the Ampulla of Vater, with a Report of Two Cases, Ann. Surg. **56**:710, 1912.

29. Rixford, cited by Outerbridge.[14]

30. Kausch, W.: Das Carcinom der Papilla duodeni und seine radikale Entfernung, Beitr. z. klin. Chir. **78**:439, 1912.

31. Hirschel, cited by Pallin, G.: Carcinom des Ductus hepaticocholedochus und seine chirurgische Behandlung (52 schwedische Fälle), Beitr. z. klin. Chir. **121**:84, 1920.

32. Tenani, O.: Surgery of the Papilla of Vater, Policlinico (sez. chir.) **22**: 291, 1922.

Hirschel performed circular resection of the duodenum with end to end suture, choledochoduodenostomy with a tube, resection of a part of the pancreas and pancreaticoduodenostomy and gastro-enterostomy. This extensive procedure was accomplished in the remarkable time of one hour. Since few surgeons could hope to equal this feat, one must agree with Cohen and Colp, from whose paper this material was reviewed, that it would be more practical to perform this operation in two stages, the first of which should be a drainage operation to eliminate the biliary obstruction and thus to get the patient into the proper physical condition to withstand the more exhausting second operation.

The fact that there are only 4 recorded cases in which reimplantation of the head of the pancreas or duct was successfully carried out after resection of the second portion of the duodenum would indicate the extreme hazard of this operation. According to Whipple, Parsons and Mullins,[33] two factors have been responsible for the mortality:

> The first was the mistaken belief that the flow of pancreatic juice is essential to life. This had led surgeons to attempt to reëstablish this flow into the duodenum or jejunum by implanting the resected head of the pancreas or the cut end of the duct into the upper intestine. The activation of the pancreatic ferments by duodenal contents compromised any type of anastomosis in the human subject, especially around the posterior aspect of the duodenum devoid of peritoneum. . . . The second factor was the attempt to carry out the excision of these tumors in one stage. . . .

The technic which they have evolved in their experience with 3 cases of carcinoma of the ampulla embodies the following principles: (1) resection of the descending loop of the duodenum with the pancreas wide of the growth, with no attempt to reestablish the continuity of the duodenum or of the pancreas with the intestine, and (2) division of the operation into two stages. At the first stage, posterior gastroenterostomy is performed, the common duct is ligated and sectioned below the cystic duct and a cholecystogastrostomy stoma is made in the anterior surface of the stomach, well away from the pylorus, an anastomotic opening at least 2 cm. in diameter being used in order to avoid subsequent stenosis and cholangeitis. At the second stage the descending portion of the duodenum is resected with inversion of the upper and lower ends, and a V-shaped portion of the head of the pancreas is resected together with the common duct. The pancreatic ducts are divided and ligated, and the cut surfaces of the pancreas are carefully approximated. Whipple, Parsons and Mullins have carried out this procedure on 3 patients. The first patient died eight months after the radical operation, following a sequence of events which included stenosis

33. Whipple, A. O.; Parsons, W. B., and Mullins, C. R.: Treatment of Carcinoma of the Ampulla of Vater, Ann. Surg. **102**:763. 1935.

of the cholecystogastrostomy opening, biliary stasis, infection and septicemia. The other 2 patients suffered no disturbance due to lack of pancreatic ferments. The utilization and absorption of fat in both cases were from 85 to 90 per cent, and the patients regained and maintained their normal weight three and seven months after operation.

Carcinoma of the infra-ampullary portion arises most often close to the duodenojejunal junction. This localization requires resection of the affected segment and reestablishment of the continuity of the intestine by end to end anastomosis or by duodenojejunostomy. End to end anastomosis is often impossible because of the necessity of resecting such a large extent of the duodenum that the ends cannot be approximated (fig. 5). The hazards of this operation are further increased by reason of the edema, hypertrophy and dilatation of the duodenal segment above the obstruction. The marked difference in the caliber of the two segments, the shrinkage of the proximal segment after relief of the obstruction and the strain caused by the rapid peristalsis of this region all increase the danger of leakage at the suture line. In this situation a side to side union, if anatomically feasible, is to be preferred.

In a somewhat analogous situation, Carter [34] resected a carcinoma of the jejunum located 6 inches (15 cm.) below the ligament of Treitz and performed a side to side duodenojejunostomy. He incised the anterior leaf of the transverse mesocolon and swung the distal portion of the jejunum to the right, contraclockwise, to lie beside the terminal portion of the duodenum, which was brought down through a slit in the mesocolon. He then completed a side to side anastomosis (fig. 5). Where so much of the duodenum has been resected that no form of duodenojejunostomy is possible, one must be content with gastro-enterostomy. This procedure, of course, is followed by regurgitation of bile and pancreatic juice into the stomach, and nausea and discomfort may be troublesome unless the stomach is thoroughly washed out daily.

PALLIATIVE OPERATIONS

Palliative operations are distinctly worth while in cases of inoperable cancer. Not only do they prolong life, but they spare the patient the suffering which precedes death by duodenal or biliary obstruction. Patients with inoperable carcinoma of the supra-ampullary portion of the duodenum may be greatly relieved by gastro-enterostomy, with or without an exclusion of the pylorus. Inoperable cancer of the peri-ampullary portion requires gastro-enterostomy and cholecystogastrostomy, cholecystoduodenostomy, cholecystenterostomy or cholecystostomy. Cancer of the infra-ampullary portion, accompanied by obstruction, may require cholecystogastrostomy and gastro-enterostomy.

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34. Carter, R. F.: Carcinoma of the Jejunum, Ann. Surg. **102**:1019, 1935.

IRRADIATION FOR CANCER OF THE DUODENUM

Irradiation has not played a prominent part in the treatment of duodenal carcinoma. Most of the tumors are of the adult, differentiated type and not likely to respond to any dose of external radiation which can be tolerated by the overlying skin. Rarely an anaplastic tumor is encountered (as in our case 2), which may temporarily respond to external radiation. The literature contains reports of a few cases in which the surgeon at the time of operation placed radium capsules in the end of a duodenal tube introduced into the duodenum by way of the mouth, so as to lie in contact with the lesion for several hours and

TABLE 4.—*Operative Results*

Patient	Location of Growth	Hospital	Operation	Result
M. B.	Supra-ampullary	Memorial	Posterior gastro-enterostomy	Death due to bilateral surgical parotitis 4 days later
D. H.	Infra-ampullary	Memorial	Exploratory laparotomy and insertion of gold radon seeds	Death 4 days later
B. K.	Periampullary	Memorial	Exploratory laparotomy, duodenotomy and biopsy	Death 11 days later; fecal fistula, peritonitis and bronchopneumonia
S. A.	Periampullary	Post-Graduate	Biopsy, posterior gastro-enterostomy and chole-cystogastrostomy	Recovery; patient untraced later
J. R.	Infra-ampullary	Post-Graduate	Gastro-enterostomy	Recovery; patient untraced later
W. F.	Infra-ampullary	Post-Graduate	Jejunostomy	Death 12 days later
G. B.	Infra-ampullary	Post-Graduate	Cholecystogastrostomy and gastro-enterostomy	Recovery; lived 2 yr.
H. S.	Supra-ampullary	Lenox Hill	Posterior gastro-enterostomy	Recovery; patient untraced
A. B.	Periampullary	Lenox Hill	Cholecystostomy, first stage; duodenotomy and excision of tumor at second stage	Death 6 hr. later
H. B.	Infra-ampullary	Polyclinic	Anterior gastro-enterostomy	Leakage at suture line; death due to peritonitis
E. D.	Periampullary	St. John's, Long Island City	Cholecystostomy, duodenotomy and biopsy	Death 3 days later due to bronchopneumonia
F. K.	Periampullary	New Haven, New Haven, Conn.	Cholecystostomy and duodenotomy and biopsy	Recovery; death 14 wk. later

later be withdrawn. Gold radon seeds have occasionally been inserted into the primary tumor (case 2). None of these procedures have been of much benefit, while the hazards of duodenal fistula, peritonitis and acute pancreatitis are great.

OPERATIVE RESULTS

Operation was performed in 12 of the 18 cases of carcinoma of the duodenum in this series. In only 1 was it possible to attempt to remove the growth. In this instance (case 16) cholecystostomy was performed as a first stage operation. At the second stage, the duodenum was opened, and a small periampullary carcinoma was excised. Death occurred six hours later.

Gold radon seeds were inserted into 1 inoperable tumor (case 2), which had previously undergone marked regression after roentgen therapy. The patient died four days later.

There were 5 postoperative recoveries (41.6 per cent). The location of the tumor and the procedure employed were as follows: (1) carcinoma of the supra-ampullary portion, posterior gastro-enterostomy; (2) carcinoma of the periampullary portion, biopsy, posterior gastro-enterostomy and cholecystogastrostomy; (3) carcinoma of the infra-ampullary portion, gastro-enterostomy; (4) carcinoma of the periampullary portion, cholecystostomy, duodenotomy and biopsy, and carcinoma of the periampullary portion, cholecystogastrostomy and gastro-enterostomy.

There were 7 postoperative deaths (58.3 per cent). The location of the lesion and the operative procedures employed were as follows: (1) carcinoma of the supra-ampullary portion, posterior gastro-enterostomy; (2) carcinoma of the infra-ampullary portion, insertion of gold radon seeds; (3) carcinoma of the periampullary portion, duodenotomy and biopsy; (4) carcinoma of the infra-ampullary portion, anterior gastro-enterostomy; (5) carcinoma of the periampullary portion, cholecystostomy, duodenotomy and biopsy; (6) carcinoma of the periampullary portion, second stage duodenotomy and excision of the growth, and (7) carcinoma of the infra-ampullary portion, jejunostomy.

In 4 instances the duodenum was opened. Specimens for biopsy were taken in 3 instances, and in the fourth case the tumor was excised. Three of these patients died. The causes of death were, respectively, peritonitis, bronchopneumonia and shock.

Of the 5 patients who survived operation, 2 were not traced. One lived fourteen weeks and died at home. The 2 remaining patients (in whom the growth was not removed) lived two years.

SUMMARY

This paper presents a clinical and roentgenographic study of 18 cases of primary carcinoma of the duodenum collected from the material of the Memorial Hospital for the Treatment of Cancer and Allied Diseases, the New York Polyclinic Medical School and Hospital, the New York Post-Graduate Medical School and Hospital, the Lenox Hill Hospital and St. John's Long Island City Hospital, all of New York; the Paterson General Hospital, Paterson, N. J., and the New Haven Hospital, New Haven, Conn. In 5 of the cases the patient was studied during life by us. All were instances of true carcinoma of the duodenal mucosa. Cases of carcinoma of the ampulla or of the papilla of Vater are not included.

The rarity of primary carcinoma is indicated by its incidence of 0.033 per cent of 350,286 autopsies. The sex incidence shows a preponderance of males of 3:1.

The usual pathologic type is some form of adenocarcinoma arising from the duodenal mucosa. The gross forms may be scirrhous, bulky and polypoid, or colloid. The pathologic findings in these 18 cases are summarized in table 1.

The symptoms of duodenal carcinoma are chiefly those due to obstruction of the duodenum and neighboring structures. The early stages are featured by anorexia, gaseous eructations, epigastric distention and nausea. As obstruction develops, these become more severe, and pain, vomiting, dehydration, loss of weight and constipation quickly follow. A palpable tumor is found in more than half the cases. The sloughing away of portions of the tumor may temporarily relieve the obstruction or give rise to severe hemorrhage. When the bile passages are obstructed, jaundice of a constant, unremitting type develops. The progress of the disease is swift, and the loss of weight may be extreme.

The average duration of life is about seven months after the onset of symptoms. The shortest duration of life is found in cases in which the lesion is around the ampulla; the longest duration, in those in which the lesion is in the first portion of the duodenum.

In almost every case of duodenal carcinoma which is studied roentgenographically definite pathologic changes can be demonstrated. Such evidence was present on the films in 15 cases in which such studies were made. In 14 of these the pathologic process was recognized and described. In only 1 instance, however, was the possibility of a primary carcinoma of the duodenum suggested. The various roentgenographic findings are described at length and summarized in table 2.

The diagnosis and differential diagnosis are discussed in detail.

The treatment of primary carcinoma of the duodenum is preeminently surgical. The operative mortality is high. In a large percentage of cases at operation there is no evidence of metastasis or local extension of the disease. The surgical removal of all of the malignant tissue might therefore often be feasible if this mortality could be brought down to a reasonable level by efforts to combat the effects of the intestinal and biliary obstructions prior to operation. The patients show advanced degrees of starvation, dehydration, alkalosis, anemia, jaundice and gastric distention. Measures recommended in the preparation of the patient for operation are the restoration of body fluids, mineral salts, carbohydrates and blood supply. Various surgical procedures which have been employed are described, discussed and illustrated. The operative results obtained in the various procedures employed in 12 of this series of 18 cases are described and summarized.

REPORT OF CASES

CASE 1.—M. B., a woman aged 48, was admitted to the Memorial Hospital complaining of epigastric pain radiating to the back. The pain was of four months' duration and was severe and cramplike. It was intensified or precipitated by the taking of food, but was not relieved by alkalis and was not accompanied by vomiting. The patient's appetite was good, but she feared to eat because of the pain thus initiated. Loss in weight was moderate but progressive. Physical examination revealed an emaciated woman of 48. The abdomen was sunken, and a hard, smooth, movable mass 5 cm. in diameter could be palpated in the midline immediately above the umbilicus. The liver was not palpable. Roentgenographic and fluoroscopic examination of the gastro-intestinal tract revealed a constant widening of the pyloric sphincter and irregularity in the outline of its surfaces. The duodenal cap was small and slightly deformed but fairly well filled. Beyond the cap there was some irregularity in the outline and distribution of the barium sulfate in the lumen, but the remaining portions appeared normal (fig. 6). Peristalsis was active; there was little delay in the passage of the barium, and no gastric retention was present after six hours. The constant widening of the pylorus was interpreted as suggestive of an annular carcinoma or a fibrotic process as the result of an old pyloric ulcer. Gastric analysis showed normal amounts of free hydrochloric acid. A clinical diagnosis of carcinoma of the pylorus was made. At operation a tumor 5 by 4 by 4 cm. was found involving the posterior wall of the duodenum immediately distal to the pylorus. The tumor had invaded the pancreas, rendering its removal impossible. Posterior gastro-enterostomy was performed, and the abdomen was closed. Four days after operation bilateral parotitis developed, and the swellings became so great that they compressed the pharynx and caused extreme dysphagia and dyspnea. The respiratory difficulty was relieved by an emergency tracheotomy, but death occurred two hours later.

At autopsy a hard ulcerated mass 5 by 4 by 4 cm. was found in the first portion of the duodenum 2 cm. below the pylorus. Metastatic masses were found in the mesenteric nodes of the duodenum, transverse colon and rectum. The liver was not involved. Microscopic examination of the duodenal tumor revealed a malignant adenoma.

CASE 2.—D. H., a woman aged 28, had attacks of severe epigastric pain in August 1929. These were accompanied by nausea and vomiting; during the next two months there was marked loss of weight and strength. Her physician discovered an oval mass in the upper part of the abdomen slightly to the left of the midline. An exploratory laparotomy at the Brownsville and East New York Hospital in December 1929 disclosed a mass the size of an orange at the duodenojejunal angle, apparently retroperitoneal in location. No specimen was taken for biopsy. A clinical diagnosis of retroperitoneal lymphosarcoma was made. Immediately after convalescence the patient received twelve treatments by high voltage roentgen therapy. This was followed by the complete disappearance of the abdominal tumor; she gained 20 pounds (9 Kg.) and was restored to her former strength. All symptoms disappeared temporarily, but six months later the tumor recurred and soon reached the size of a grapefruit. Recourse again was had to roentgen therapy, but the tumor did not respond. Symptoms increased in severity, and the patient was referred to the Memorial Hospital. Roentgenograms of the gastro-intestinal tract showed no deformity of the duodenal cap or retention of barium after six hours. The curving loop made by the course of the duodenum, however, was greatly widened as though the expansive growth of a tumor in that location had thrust the duodenum aside (fig. 7). A diagnosis of retroperitoneal sarcoma

or carcinoma of the head of the pancreas was made, and an exploratory laparotomy was performed by Dr. Frank E. Adair. A rounded, globular tumor mass containing several cystic areas was found apparently retroperitoneally beneath the duodenum and the jejunum. It was impossible to remove the mass, and an attempt was therefore made to accomplish its destruction with interstitial radiation. Twenty-two gold radon seeds containing 55.51 millicuries of radon were inserted into the mass and spaced 1 cm. apart. The patient's condition postoperatively was poor, and death occurred four days later. At autopsy a mass of cancerous tissue was found completely surrounding the duodenum and causing partial constriction. The tumor tissue was white, opaque and partly necrotic as a result of the irradiation. Its texture suggested lymphosarcoma. The mesenteric nodes and the liver were not involved. The stomach was greatly dilated. Microscopic study showed a primary anaplastic adenocarcinoma of the duodenum (fig. 8).

CASE 3.—B. K., a woman aged 60, presented a history of "stomach trouble" for the past five years. Four months before she came to the Memorial Hospital there developed pain in the right upper quadrant, anorexia, loss of weight and moderate constipation. Roentgenograms made elsewhere and not available for study were said to have shown carcinoma of the hepatic flexure of the colon. At this time the patient noted marked feeling of distention after eating. Physical examination disclosed the following abnormal findings: emaciation, dehydration, anemia, edema of the extremities and a slightly movable, irregular, nontender mass the size of an orange in the region of the right kidney. Urologic studies showed diminished function of the right kidney, with many pus cells in the urine. A pyelogram showed changes interpreted as a destructive process in the right kidney, probably inflammatory in nature. A roentgenographic study of the gastrointestinal tract disclosed a filling defect in the prepyloric segment of the stomach and evidence of upward displacement of the duodenum, pressure on the greater curvature of the gastric antrum, with filling defects in the stomach and duodenum. Some evidence of infiltration of the pylorus and in the descending portion of the duodenum was noted. There was marked retention after six hours (fig. 9). These findings were interpreted as possibly being caused by a tumor of the head of the pancreas. Exploratory laparotomy revealed a large mass 6 by 4 cm. in diameter adherent to the posterior surface of the stomach, apparently arising from the duodenum and impossible to remove. The duodenum was opened, a biopsy specimen was removed, and the duodenum was closed with silk sutures. The abdomen was closed; on the sixth postoperative day bronchopneumonia developed, and the patient died five days later.

Autopsy disclosed focal and pelvic peritonitis as the results of a breakdown of the suture line in the duodenum, a fecal fistula and bronchopneumonia. Surrounding the ampulla of Vater and extending for 6 cm. along the lumen and partly obstructing it, was an annular, polypoid primary carcinoma of the duodenum. There was no evidence of metastases. Microscopic study showed primary malignant adenoma of the duodenum (fig. 11).

CASE 4.—C. S., a woman aged 47, was admitted to the Memorial Hospital on Feb. 17, 1931, with the complaint of weakness, loss of weight, fatigue, nausea and vomiting. These symptoms had arisen four months before and had steadily become more marked. The vomiting appeared to have no relation to meals, and the vomitus usually contained bile. There had been no jaundice until a few weeks prior to admission, when a transitory attack occurred, accompanied by fever. During the past twelve years there had been many attacks of pyuria. Examination disclosed a middle-aged woman in fair general condition. In the right

upper quadrant of the abdomen a mass was palpable which appeared to be an enlarged right kidney. A pyelogram showed hydronephrosis of the right kidney. On February 28 the right kidney was removed by Dr. Benjamin Barringer. The specimen contained a broken-down hypernephroma measuring 8 by 7 by 5 cm., the bulk of which showed gross caseous necrosis. The renal pelvis was dilated at the lower pole, where there was marked hydronephrosis. The microscopic diagnosis was "papillary adenocarcinoma of the renal tubule type, with clear and granular cells." The patient made a smooth recovery and felt moderately better for about six weeks, after which there was a return of weakness, nausea and vomiting. She lost weight rapidly, and in June 1931, four months after operation, increasing jaundice, anemia and fever developed. Vomiting of bile-stained fluid became more frequent. She received a transfusion of blood, and for a time improved in general health. Late in July her temperature rose daily to 104 F., accompanied by chills and a steadily increasing jaundice. The stools became clay colored and offensive. Vomiting occurred several times a day, and the vomitus often contained clots of blood as well as coffee-ground material. When readmitted to the Memorial Hospital at this time she was profoundly ill and deeply jaundiced and had lost a great deal of weight. She complained of a dull pain in the epigastrium, which was relieved only by vomiting. The urine was highly colored with bile and hemoglobin. The temperature during the chills rose to 105 F. and occasionally to 106 F. The patient was greatly dehydrated and appeared to be moribund. Large amounts of fluids and dextrose were administered intravenously. The blood count on admission showed 1,550,000 red cells, 14,400 white cells and a hemoglobin content of 40 per cent. The differential count showed 91 per cent polymorphonuclear leukocytes. Three transfusions of a total of 1,950 cc. of whole blood were given within forty-eight hours after admission. The stomach was greatly dilated, and large quantities of blood-stained fluid were removed by gastric lavage. This fluid contained identifiable patches of desquamated gastric mucosa. An attempt at duodenal drainage failed to demonstrate evidence of the patency of the common bile duct. The patient's condition was extremely poor. Vomiting of bright red blood occurred on two occasions, after which the patient grew rapidly weaker and died. No definite diagnosis was made prior to death, although the general picture appeared to indicate a high degree of biliary obstruction and infection. The most likely cause for this was thought to have been a recurrence of the hypernephroma of the right kidney. Roentgenograms made several weeks prior to the last admission showed hypomotility, a large duodenal cap and an irregular outline of the second portion, indicating partial duodenal obstruction.

Autopsy revealed an extreme degree of jaundice; the liver was normal in size, dark green and markedly congested. The gallbladder, common bile duct and hepatic ducts were greatly dilated. One could readily pass a finger down the common bile duct to the ampulla of Vater, which was obstructed by a mass within the duodenum. The stomach was distended to three times its normal size, and the pylorus was widely dilated (fig. 14). The first portion of the duodenum was similarly widely distended. Ten centimeters from the pylorus there was a large, papillary, ulcerated growth involving the entire circumference of the duodenum and extending along the lumen for a distance of 6 cm. This tumor surrounded the ampulla of Vater and completely obstructed it, so that the common duct and the remainder of the biliary system were greatly dilated. There was no evidence of any metastases anywhere in the body and no evidence of any recurrence of the previous hypernephroma of the right kidney. Microscopic study of the tumor of the duodenum showed a primary malignant adenoma (fig. 9). Com-

parison of the duodenal tumor with the mass previously removed with the right kidney (fig. 12) showed them to be two histologically distinct tumors, and it was the opinion of Drs. Ewing and Stewart that this was a proved example of multiple primary malignant growth.

CASE 5.—H. S., a white German woman aged 68, was admitted to the Lenox Hill Hospital on Nov. 4, 1932, complaining of pain in the epigastrium, vomiting, loss of 20 pounds (9 Kg.) in weight and increasing weakness. Symptoms were of three months' duration. On one occasion eight months prior to admission and five months before the onset of symptoms she noted bright red blood in the stools. Examination showed a thin, pale elderly woman, who had evidently lost considerable weight. The edge of the liver was barely palpable. There was a slightly palpable tender mass in the midepigastrium. The stomach was dilated, and an audible splash could be demonstrated. A roentgenographic study of the gastro-intestinal tract disclosed a persistent filling defect in the duodenum at the junction of the first and the second portion. The duodenal wall was markedly rigid, and the filling defect was persistent and caused considerable obstruction, so that at the forty-eighth hour considerable barium was retained within the stomach. The report made by Drs. William H. Stewart and H. E. Illick suggested the possibility of malignant obstruction of the duodenum. On November 9 the abdomen was explored by Dr. Herman Fischer, who found the stomach to be greatly dilated and its walls markedly hypertrophied. The pyloric ring was normal. Beginning on the distal side of the ring and involving the first and second portions of the duodenum was a hard, elastic, whitish tumor tissue which Dr. Fischer considered unquestionably malignant and not inflammatory. There was no evidence of metastases or local extension. A posterior gastro-enterostomy was performed. No biopsy was made. The postoperative course was smooth, and the patient left the hospital in relatively good condition. Two years later reexamination showed the gastro-enterostomy stoma functioning well. There was a constant rounded shadow present which deformed the duodenum and prepyloric area of the stomach. This was considered to be the greatly increased size of the mass found at operation.

CASE 6.—L. H., a 70 year old German woman, was admitted to the Lenox Hill Hospital to the service of Dr. Carl Theobald in December 1930, complaining of persistent vomiting and a viselike pain around the upper portion of the abdomen and epigastrium of five weeks' duration. This pain usually subsided after the stomach had been emptied by vomiting. The patient had never been jaundiced. Examination revealed an elderly, emaciated woman in poor physical condition. The stomach was greatly distended, as indicated by marked tympany over most of the abdomen. The diagnosis on admission was obstruction of the pylorus of unknown etiology. After the administration of large amounts of fluids and stimulants, the stomach was emptied by lavage. A roentgenographic study of the gastro-intestinal tract revealed a high grade pyloric obstruction, so that at the sixth hour only 10 per cent of the barium had passed out of the stomach. The character of the obstruction could not be determined from the roentgenograms, although a malignant growth and ulcer were suggested as the most likely causes. Three days later the patient suddenly became weaker and cyanosed, the temperature remained elevated, the pulse grew feeble and she died, apparently of a terminal myocardial failure.

At autopsy the gallbladder was found adherent to the duodenum and communicating with it through a spontaneous cholecystoduodenostomy opening. The stomach was greatly dilated, with thickening of the wall in the pyloric region. The first portion of the duodenum immediately distal to the pylorus was obstructed

by an ulcer with a raised necrotic border and base. The surrounding area was indurated and infiltrated. There were no evidences of metastases. The lumen of the small intestine was filled with a large amount of red blood.

Microscopic examination of the ulcerated tumor of the duodenum disclosed adenocarcinoma containing a few areas of anaplastic squamous carcinoma. This case was briefly referred to by Sauer [35] in a discussion of the possibility of carcinoma of the duodenum arising on the basis of a previous duodenal ulcer.

CASE 7.—M. B., a French woman aged 51, was admitted to the Lenox Hill Hospital on Aug. 28, 1930, complaining of loss of weight, weakness, nausea and vomiting of three months' duration. At the time of admission she had lost 40 pounds (18 Kg.) in weight, and the attacks of vomiting occurred several times a day precipitated by the taking of any food or drink. Examination disclosed an obese white woman whose skin was a muddy yellow. She was drowsy, weak and dehydrated because of severe vomiting. Study of the blood chemistry revealed a marked increase in all constituents, probably due to dehydration. The carbon dioxide-combining power was 73.9. Examination of the gastro-intestinal tract revealed no changes recognizable as cancer or ulcer. There was no roentgenographic indication of obstruction anywhere. The patient's condition became steadily worse despite all efforts, and she died six days after admission.

At autopsy the stomach was greatly dilated with gas. In the left upper quadrant of the abdomen was a tumor involving the distal portion of the duodenum and the proximal portion of the jejunum, which was bound down tightly to the splenic flexure and to the transverse colon. The lumen of the duodenum was almost completely occluded by a polypoid tumor, which was extensively ulcerated. This tumor was soft and invaded the duodenal wall in many areas and formed nodules on its outer surface. It encircled the entire duodenum and measured 11 cm. on its long axis. There was no involvement of the liver, nodes or any other structures.

Microscopic study of the tumor showed a small cell adenocarcinoma with extensive areas of spontaneous necrosis.

CASE 8.—C. A., a housewife aged 52, entered the New York Polyclinic Medical School and Hospital on Feb. 18, 1932, complaining of jaundice and pain in the epigastrium. Six weeks previously she noted that her skin and conjunctivae were yellow. Three days later she experienced pain in the right upper quadrant, which she described as "feeling like a dead weight." Soon afterward she had attacks of nausea and vomiting. For the past three months she had a distaste for fats and lost weight and strength. The stools were bloody; constipation steadily increased. The patient was treated by administration of fluids and dextrose and other supportive measures but died one week after admission. Because of her moribund condition no roentgen studies were made of the gastro-intestinal tract except for films of the gallbladder, which were unsatisfactory for diagnosis, because of respiratory movements.

Autopsy, performed by Dr. Aaron S. Price, disclosed a jaundiced, emaciated woman. The stomach was enormously dilated. The gallbladder was dilated to a diameter of 8 cm. Arising in the periampullary portion of the duodenum was a carcinoma which had obstructed the ampulla and had secondarily invaded the pancreas. Microscopic study of the tumor showed malignant adenoma and adenocarcinoma, partly diffuse, arising from mucous glands with tendencies toward squamous metaplasia (fig. 18).

35. Sauer, P. K.: Carcinoma Following Gastric and Duodenal Ulcer, Ann. Surg. **102**:295, 1935.

CASE 9.—H. B., a man 78 years old, was admitted to the New York Polyclinic Medical School and Hospital on Feb. 23, 1931, complaining of pain in the epigastrium, loss of weight, nausea and vomiting after taking food. The vomitus was greenish and copious, and vomiting was followed by marked symptomatic relief. These symptoms were of six weeks' duration, during which time he had lost 25 pounds (11 Kg.) in weight. Constipation was of long standing. Physical examination disclosed an elderly man, chronically ill, disoriented, dehydrated and feeble. An irregular mass was palpable in the epigastrium. The stomach was greatly dilated and was boldly outlined through the abdominal wall. The intern made a note that despite negative roentgenograms said to have been made elsewhere prior to admission, he believed that the patient had an obstruction somewhere in the duodenum, either from a new growth or from adhesions. A serial roentgenographic study of the gastro-intestinal tract showed "gastric retention due to obstruction of the duodenum, probably caused by adhesions of the second and fourth portions. Involvement of the pancreas should be suspected. The changes found may be due to pancreatitis, ulcer of the duodenum, or tuberculous infection of the peritoneum." The patient was in extremely poor condition. After great efforts to get him in condition for operation by administration of dextrose and fluids by all routes, a laparotomy was done by Dr. Robert E. Brennan with the patient under spinal anesthesia, and an anterior gastro-enterostomy with entero-enterostomy was performed. The patient died several days later.

Autopsy, performed by Dr. Aaron S. Price, disclosed diffuse peritonitis apparently arising from the region of the gastro-enterostomy. The intestine was semigangrenous, with no attempt at healing. In the terminal portion of the duodenum, just above the duodenojejunal junction, was a hard white tumor which had ulcerated and encircled the lumen to produce almost total obstruction. The proximal portion of the duodenum and the stomach were dilated. There was no evidence of local extension or metastases. Microscopic study showed adenocarcinoma arising from cells of the glands of Lieberkühn.

CASE 10.—A. B., a man aged 71, entered the Paterson General Hospital complaining of dizzy spells, sudden transitory attacks of unconsciousness, a feeling of constriction in the esophagus and frequent attacks of dyspepsia with gaseous eructations. There was no history of vomiting or of gross blood in the stools. During the past several months there had been some progressive enlargement of the abdomen. Examination revealed a large indirect inguinal hernia and a hydrocele on the right side and moderate abdominal ascites. No operation was performed except paracentesis. Examination of the stools showed the presence of blood. Roentgenographic studies of the gastro-intestinal tract made after the administration of barium showed that the stomach was not dilated and that peristalsis was active. The first portion of the duodenum was obscured by the antrum of the stomach. The second portion was irregularly deformed and narrowed. No definite diagnosis was made. Permission for exploratory laparotomy was refused. Three months later the patient died.

Autopsy disclosed a broad, annular, papillary and infiltrating carcinoma, 8 cm. in diameter, completely encircling the lumen of the duodenum, arising at a point 1 cm. below the papilla of Vater. The mass was ulcerated and firm and had a border 3 cm. in thickness. There were miliary metastases to the visceral and parietal peritoneum, liver and lymph nodes. Microscopic study showed adenocarcinoma of the duodenum, grade 2. (Dr. William Wuester and Dr. A. Hobson Davis of the Paterson General Hospital permitted us to report this case.)

CASE 11.—S. A., an Italian youth 18 years of age, was admitted to the New York Post-Graduate Medical School and Hospital on March 2, 1915, complaining of pain in the epigastrium, loss of weight and a mass in the epigastrium. The first symptom of epigastric pain developed one year prior to admission and was consistently aggravated by eating. Physical examination revealed a fairly well nourished, anemic youth. There was no jaundice. In the epigastrium, slightly to the right of the midline, a hard mass about 5 cm. in diameter could be palpated. The mass was slightly movable, particularly with respiration. The liver was not enlarged, although an enlarged gallbladder could be palpated close to the hard mass already described. Four weeks after admission the skin and conjunctivae showed jaundice, which within two weeks increased markedly. The stools became pale and the urine was dark with bile. A roentgenogram of the region of the gallbladder showed a shadow of an enlarged viscus but no stone. A serial roentgenographic study of the gastro-intestinal tract showed irregularity of the second portion of the duodenum, which curved far out to the right. In the middle of the first portion of the duodenum there was noted a persistent fleck of bismuth, which was still present six hours later. At this time there was a small gastric residue. The findings were interpreted as a perforating ulcer of the inferior horizontal portion of the duodenum. On March 23 the abdomen was explored by Dr. John Erdmann, who found a tumor, 8 cm. in diameter, in the second part of the duodenum, surrounding the ampulla of Vater. A large piece of the tumor was excised for biopsy, and posterior gastro-enterostomy and cholecystogastrostomy were performed. There was no evidence of extension or metastases at operation. The postoperative course was smooth, and the patient was discharged from the hospital much improved three weeks later. He never returned for examination and remained untraced. Pathologic examination of the biopsy specimen showed a smooth, lobulated mass, measuring 4 by 3 by 2 cm. Microscopic study showed a fairly aggressive adenocarcinoma growing in disorderly fashion in a fibrous stroma.

CASE 12.—E. D., a woman aged 56, was admitted to St. John's Long Island City Hospital on March 6, 1935, under the care of Dr. Emanuel F. Kalina, complaining of loss of weight, appetite and strength and of chills, fever and jaundice. Two months prior to her illness she began to have pains in the limbs and fever, chills and profuse perspiration. The temperature ranged from 102 to 104 F. The stools became pale, soft or watery, and the skin and conjunctivae became jaundiced. The ingestion of food brought on sour eructations, distention of the epigastrium, nausea and belching of gas, but no vomiting. Examination disclosed jaundice, loss of weight, tenderness in the epigastrium and muscular spasm over the area of the gallbladder. The liver and gallbladder were not palpable. The red cell count was 3,080,000, the white cell count 26,300 and the hemoglobin content, 51 per cent. The icteric index was 35. The van den Bergh direct reaction was positive in thirty seconds. Occult blood was present in the stools. Roentgenograms of the gastro-intestinal tract made after a barium meal showed a normal stomach. The duodenal cap was greatly enlarged, triangular in shape and regular in outline. The descending portion was irregular and narrowed, and barium was retained in the second portion for more than twenty-four hours (figs. 21, 22 and 23). These findings were interpreted as indicating a duodenal diverticulum with partial obstruction. In view of the symptoms of jaundice and fever, indicating biliary obstruction, and the appearance of the duodenum in the films, a diagnosis of possible carcinoma of the head of the pancreas was considered, and exploratory laparotomy was advised. At operation by Dr. William J. Lavelle a markedly distended gallbladder was found. A mass was palpated in the second

portion of the duodenum. This was exposed through a small incision and found to be a polypoid carcinoma surrounding the region of the ampulla. The proximal portion of the duodenum was greatly dilated. The duodenal obstruction was partly relieved by freeing adhesive bands in the region of the growth. A portion was excised for biopsy, and the duodenum was closed in two layers. A rubber drainage tube was inserted into the gallbladder and brought out through the incision. Postoperatively, there was profuse drainage of bile from the tube and from a Levine tube introduced into the stomach through the mouth. On the third postoperative day, bronchopneumonia developed, and the patient died four days later.

Autopsy disclosed a friable, polypoid tumor surrounding the region of the papilla but arising in the duodenum (fig. 24). The gallbladder and common duct were dilated. The liver was smooth and green. There was no evidence of local extensions or metastases. The suture line around the opening in the duodenum was intact. Microscopic study of the specimen showed a papillary adenocarcinoma of the duodenum (fig. 25).

CASE 13.—J. R., a man aged 51, complained of sour stomach and heartburn of two years' duration, with nausea, vomiting and epigastric pain of eight weeks' duration. Six weeks prior to admission a roentgenographic study of the gastro-intestinal tract revealed retention of barium after six hours. He had lost 30 pounds (13.6 Kg.) in the past six weeks, his weight falling from 171 to 141 pounds (77.6 to 64 Kg.). Physical examination showed a markedly emaciated patient. Urinalysis showed the presence of sugar. Roentgenograms of the gastro-intestinal tract revealed obstruction of the third portion of the duodenum with marked dilatation of the entire duodenum and retention of barium within the stomach and duodenum after six hours (fig. 26). A diagnosis of duodenal obstruction was made. The operation was performed by Dr. John F. Erdmann, on May 25, 1929, and a carcinoma of the terminal portion of the duodenum was found. There were multiple metastases found in the liver. A gastro-enterostomy was done, and the patient was discharged from the hospital nineteen days later. He subsequently was untraced.

CASE 14.—W. F., a man aged 45, complained of nausea, vomiting, epigastric pain and distention. Previous examination at another hospital had not yielded a definite diagnosis, and an exploratory laparotomy had been advised. A roentgenographic series of the gastro-intestinal tract showed the terminal portion of the duodenum distinctly outlined by the barium in a manner which suggested some obstruction of the lumen, but this escaped detection at the time and was noted only after the patient had been operated on. Dr. Erdmann's clinical diagnosis was carcinoma of the liver with generalized abdominal carcinomatosis. At operation on Sept. 21, 1927, a definite carcinoma of the terminal portion of the duodenum was found. There was an extensive generalized carcinomatosis involving all the abdominal structures in addition to bulky metastases in the liver. A palliative jejunostomy was performed. The patient failed steadily and died twelve days after operation. Permission for autopsy was not obtained.

CASE 15.—F. K., a woman aged 36, was admitted to the New Haven Hospital on April 24, 1935, complaining of weakness, anorexia and a constant dull pain in the right upper quadrant which had been present for two months. A month prior to admission she had an attack of severe pain in the same region, associated with a progressively increasing jaundice. The pain radiated through to the back. The skin became yellow, the stools were pale and clay colored, and the patient lost weight steadily. There was no nausea, vomiting or tarry stools. Physical examination showed marked jaundice, tenderness in the region of the gallbladder, rigidity of

the abdominal muscles and enlargement of the liver. The red cell count was 4,200,000, the white cell count 13,600 and the icteric index 100. The van den Bergh test was positive. The stools were negative for occult blood or bile. A diagnosis of chronic cholecystitis and cholelithiasis was made, and on May 5 an exploratory laparotomy revealed a large, tense gallbladder and a mass in the region of the ampulla, which was thought to be an impacted stone. Because of brisk bleeding which occurred, the only procedure attempted was the insertion of a drain into the gallbladder. Twenty-six days later the abdomen was again explored in the service of Dr. S. C. Harvey, and a large friable, cauliflower mass was found surrounding the ampulla of Vater. The duodenum was opened and a biopsy specimen was removed. The postoperative course was stormy, and a fecal fistula developed in the lower angle of the wound. The patient left the hospital in poor condition, became progressively worse and was brought back to the hospital, where she died on September 9.

Autopsy disclosed a markedly emaciated woman weighing only 65 pounds (29 Kg.). There was a fecal fistula leading down to the transverse colon. The stomach was markedly distended to five times normal size and filled nearly the entire abdominal cavity. The proximal duodenum was distended to four times its normal size. The ampulla of Vater was surrounded by a friable, fungating tumor mass 3 cm. in diameter, which occluded the lumen. The lymph nodes of the celiac and peripancreatic regions were enlarged and obviously involved by metastases. The liver was not involved, although the pancreas was directly invaded. Microscopic examination of a specimen from the periampullary tumor showed an adenocarcinoma of high columnar cells.

Case 16.—A. B., a man aged 58, was admitted to the Lenox Hill Hospital, service of Dr. Robert C. Schleussner, with a complaint of attacks of fever lasting only one or two days, accompanied by chills, intermittent jaundice and tenderness in the right upper quadrant. Roentgenograms of the abdomen made without the administration of any dye showed the gallbladder clearly outlined and enlarged. This appearance was interpreted as evidence of chronic cholecystitis. Roentgenograms and fluoroscopy of the gastro-intestinal tract made after the administration of barium revealed no evidence of ulcer or cancer in the stomach or duodenum. The second portion of the duodenum, however, showed some deformity, which was considered to be due to adhesions. There was no gastric residue at six hours. Physical examination disclosed the following positive findings: moderate jaundice, fever and tenderness in the right upper quadrant. The stools did not contain bile; the urine was colored with bile. After a clinical diagnosis of impacted stone in the common duct, exploratory operation was done by Dr. Otto C. Pickhardt, and the common duct found to be obstructed at the ampulla. The dilated duct was explored, but no stone found. Because of the patient's condition it was thought inadvisable to search further for the cause of the obstruction at this stage, and the operation was terminated with the insertion of a T tube into the duct to relieve the biliary obstruction. Postoperatively there was a profuse drainage of bile from the tube, and the jaundice cleared up within a week. The condition of the patient improved slowly. Four weeks after the operation he suddenly vomited a large quantity of bright red blood and simultaneously began to bleed from the abdominal wound. A transfusion of 400 cc. of whole blood was immediately given to the patient. On the following day the wound was opened and large blood clots removed. No source of the bleeding was found. The duodenum was exposed, and a small mass was palpable in the second portion. The duodenum was opened, and a soft, friable tumor mass was found on the posterior

surface close to the ampulla. This was excised, and the duodenum was closed. There was no evidence of metastases within the abdomen. Six hours later the patient died. Microscopic examination of the specimen removed from the duodenum showed adenocarcinoma.

CASE 17.—G. B., a woman aged 45, complained of epigastric pain, nausea and vomiting. Symptoms had been present for six weeks. A roentgenographic study of the gastro-intestinal tract showed obstruction of the second portion of the duodenum. Operation by Dr. John F. Erdmann disclosed a large tumor mass which had almost completely encircled and obstructed the periampullary portion of the duodenum. The obstruction was relieved by cholecystogastrostomy and posterior gastro-enterostomy. The postoperative course was smooth, and the patient lived for two years and died at home. Permission for autopsy was not obtained.

CASE 18.—C. G., a woman aged 45, entered the Lenox Hill Hospital on Feb. 13, 1936, service of Dr. Abraham L. Garbat, complaining of intermittent fever, jaundice, pain in the right upper quadrant, pruritis, loss of weight, weakness, anorexia and vomiting. The symptoms began one year prior to admission and had persisted thereafter, except for four short remissions during that time. Roentgenograms of the gastro-intestinal tract made twelve months before admission showed no definite abnormality of the stomach or duodenum. Physical examination revealed a markedly jaundiced woman in an extremely poor condition because of sepsis, vomiting and dehydration as the consequence of biliary and duodenal obstruction. The urine was dark and contained considerable bile. The stools were clay colored and were negative for tests for bile. The icteric index was 133; the carbon dioxide-combining power was 34 volumes per cent. Analysis of the duodenal contents on seven occasions showed only slight evidence of bile. After the intravenous administration of dextrose in saline solution the patient's condition improved slightly, but two days after admission she suddenly became restless, passed into shock and died.

Autopsy disclosed a markedly jaundiced, emaciated woman about 45 years of age. When the abdomen was opened a massive hemorrhage was found behind the peritoneum, within the peritoneal cavity and inside the lumen of the small intestine. Both pleural cavities contained considerable clear fluid. The liver was dark green and enlarged and extended 5 cm. below the costal margin. The gallbladder had been removed at operation eleven years before. The bile and pancreatic ducts were greatly dilated, the common duct measuring 1.5 cm. in diameter. Surrounding the ampulla of Vater was a raised, polypoid ulcerated tumor, 2.5 cm. in diameter. There was no evidence of metastasis or extension anywhere within the abdomen. Microscopic examination of the duodenal tumor showed adenocarcinoma.

ABSTRACT OF DISCUSSION

DR. E. V. POWELL, Temple, Texas: The paper by Drs. Hoffman and Pack recalls a case that I reported to the New York Roentgen Society while I was at St. Bartholomew's Hospital. It was one of duodenal carcinoma, which I was lucky enough to diagnose as a tumor. It was an adenocarcinoma and gave a filling defect about the size of a golf-ball within the duodenal cap. Obstruction was almost, but not entirely, complete. I have since seen one other carcinoma of the duodenum which arose near the papilla and terminated fatally. In the first case operation was performed and radon seeds were implanted. The patient lived long enough to get away from the hospital, but I do not know what happened to him later.

DR. ROSS GOLDEN, New York: Drs. Hoffman and Pack's unfortunate experience with roentgen diagnosis of carcinoma of the duodenum should be a stimulus to roentgenologists. Carcinoma of the duodenum can be correctly interpreted by roentgen examination.

One of the young men of the hospital, who had only about three or four years' experience in roentgenology, correctly made such an interpretation a few years ago, based on the fact that the mucous membrane of the second portion of the duodenum was destroyed over one side. The mucosal folds of the duodenum below the first portion are marked, making that kind of an interpretation relatively easy.

One must become acutely conscious of the mucous membrane of the gastrointestinal tract. Within a year one of the residents at the hospital with which I am associated demonstrated a duodenum in which the mucous membrane was destroyed from about the beginning of the second portion clear through the second portion into the jejunum. He thought it was probably not a carcinoma and raised the question of a lymphoblastoma. The pathologist called the growth a lymphosarcoma, and the patient has improved under roentgen treatment.

CARE OF THE SEVERELY BURNED

WITH SPECIAL REFERENCE TO SKIN GRAFTING

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From my experience with the care of the severely burned, I believe that the following points are especially important: 1. During the first day or so the systemic changes assume a position of greater importance than the local injury. 2. Later in the care of the local lesion the use of fundamental principles of cleanliness and good drainage, in contradistinction to the use of this and that preparation or technic which ignores these principles, represents sound treatment. 3. Insistence on the necessity of early resurfacing of the resultant granulating surface should be stressed because of the marked decrease in the period of convalescence with its economic potentialities and the extent to which functional incapacitation from contracture or cosmetic blemishes can be forfended. 4. When the time for skin grafting is at hand, dependence on fundamental principles and methods, in contradistinction to the use of unusual types of grafts with or without a "far-fetched" method of placement, puncturing or dressing, usually will tend toward real success.

In a series of 514 skin grafts which were transplanted at 361 separate operations on 257 different persons, 299 of the grafts were transplanted at 193 separate operations on 144 different persons to alleviate the damage resulting from a burn of one type or another. Moreover, for my purpose the damage found either of a potentially deforming or of an actual contractural character in a series of burned persons presents most of the situations necessary to exemplify the principles involved in the successful grafting of skin.

EARLY CARE

In the group of 144 burned persons for whom skin grafting to a granulating surface was eventually necessary, 32 were cared for at one stage or another of a large severe acute burn. Not included in this

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From the Department of Surgery of the University of Kansas School of Medicine.

Read before the Section on Surgery, General and Abdominal, at the Eighty-Seventh Annual Session of the American Medical Association, Kansas City, Mo., May 15, 1936.

group are 5 persons, 3 of whom died within from one to three days after the burn and 2 of whom died of complications in the intermediate period before skin grafting could be completed.

Systemic Treatment.—Most of the emphasis in these cases was focused early on the alleviation of the profound systemic disturbance which occurred when the burn was of extensive proportions. In the patients seen immediately after being burned systemic treatment was based on the premise that besides considering an adequate amount of morphine for the alleviation of pain as a sine qua non and attempting to preserve normal body temperature, the salient point in the treatment was the early and more or less continuous replacement by substitution of that which had been lost and was being lost from the "circulatory tree." The work of Underhill and his co-workers [1] and Blalock [2] on the severely burned has served to draw attention to the rapid loss of blood plasma from the circulatory tree in amounts which soon may cause death. The lost plasma apparently tends to accumulate in the tissues adjacent to the area burned, and the mechanism of reabsorption tends to be rather negligible during the first thirty-six to forty-eight hours.

Main reliance for the purpose of dilution and replenishment of the fluids was placed on hypotonic saline solution. To replenish the protein lost from the circulatory fluids, autogenous blood was considered the solution nearest to that of the normal fluid. As a rough index

1. Underhill, F. P.; Carrington, G. L.; Kapsinow, R., and Pack, G. T.: Blood Concentration Changes in Extensive Superficial Burns and Their Significant Systemic Treatment, Arch. Int. Med. **32**:31-49 (July) 1923. Underhill, F. P.: The Lethal War Gases, New Haven, Conn., Yale University Press, 1920: The Physiology of Experimental Treatment of Poisoning with the Lethal War Gases, Arch. Int. Med. **23**:753-770 (June) 1919. Underhill, F. P.; Kapsinow, R., and Fisk, M. E.: Studies on the Mechanism of Water Exchange in the Animal Organism: I. The Nature and Effects of Superficial Burns, Am. J. Physiol. **95**:302-314, 1930; II. Changes in Capillary Permeability Induced by a Superficial Burn, ibid. **95**:315-324, 1930. Underhill, F. P.; Fisk, M. E., and Kapsinow, R.: III. The Extent of Edema Fluid Formation Induced by a Superficial Burn, ibid. **95**:325-329, 1930. Underhill, F. P., and Fisk, M. E.: IV. The Composition of Edema Fluid Resulting from a Superficial Burn, ibid. **95**:330-333, 1930. Underhill, F. P.; Fisk, M. E., and Kapsinow, R.: V. The Relationship of the Blood Chlorides to the Chlorides of Edema Fluid Produced by a Superficial Burn, ibid. **95**:334-338, 1930; VI. The Composition of Tissues Under the Influence of a Superficial Burn, ibid. **95**:339-348, 1930. Underhill, F. P., and Fisk, M. E.: VII. An Investigation of Dehydration Produced by Various Means, ibid. **95**:348-363, 1930; VIII. A Study of Dehydration by Pilocarpine Under Varied Dietary Conditions, ibid. **95**:364-370, 1930.

2. Blalock, Alfred: Experimental Shock: VII. The Importance of the Local Loss of Fluid in the Production of Low Blood Pressure After Burns, Arch. Surg. **22**:610-619 (April) 1931.

to the amount of solution needed, the extent [3] and severity of the burn were considered in relationship to the size and age of the patient, and by means of periodic determinations of the blood pressure and repeated estimates of the hemoglobin content, the amount of plasma lost and the degree of blood concentration were roughly estimated. In a few instances adults received as much as from 4 to 8 liters of isotonic saline solution per day. The work of Smith and Mendel [4] and of Rowntree [5] on water intoxication indicates the safety of these amounts. Sometimes, if the patient was a child with some evidence of acidosis, a 5 per cent solution of dextrose in amounts to alleviate the symptoms was considered advisable. Repeated transfusions of blood were given according to the probable degree of the loss of plasma. When the oxygen-combining power of the blood was lowered, sodium bicarbonate was given in sufficient quantities to turn the urine alkaline. Ordinarily, after the first forty-eight hours, the systemic treatment simmered down to attention to a relatively high fluid intake and output and general symptomatic care of the patient. For preservation of a normal body temperature, an overhead canopy heated by electric lights was found to be efficient.

Early Local Care.—The early local care of the wound was deemed to be important mainly in a negative way. Usually some type of fixative, such as tannic acid (most frequently), gentian violet, dehydrated alcohol, trinitrophenol or aluminum acetate, was used, but not with the idea of the fixative being of great value in the correction of the disturbance in physiologic relations but because of the cleanliness of the method and the lessened disturbance to the patient.

As Taylor [6] has noted, the too ambitious use of tanning solutions in cases of superficial burns may fix not only the dead layers of skin but any of the germinal layer and the appendages of the skin that may remain, such as the hair follicles or the sebaceous glands. To the fixa-

3. Berkow (A Method of Estimating the Extensiveness of Lesions [Burns and Scalds], Based on Surface Area Proportions, Arch. Surg. **8**:138 [Jan.] 1924) has again within recent years emphasized that for the purpose of prognosis it is important for the physician to estimate at an early time the relative area of the body surface involved.

4. Smith, A. H., and Mendel, L. B.: The Adjustment of Blood Volume After Injection of Isotonic Solutions of Varied Compositions, Am. J. Physiol. **53**:323 344, 1920.

5. Rowntree, L. G.: Water Intoxication, Arch. Int. Med. **32**:157-174 (Aug.) 1923; The Effects on Mammals of the Administration of Excessive Quantities of Water, J. Pharmacol. & Exper. Therap. **29**:135-159, 1926.

6. Taylor, Frederic: The Misuse of Tannic Acid, J. A. M. A. **106**:1143-1145 (April 4) 1936.

tion method associated with Davidson's name [7] there has been attributed by him and others [8] a decrease in mortality principally during the second twenty-four hour period. In the cases considered in this paper a decrease in mortality during this period seemed to be associated rather closely with the proper systemic management of the patient rather than with the care of the local lesions.

When proper early precautions were taken the development of a true abscess beneath the tanned crust was of rare occurrence. When a collection of pus did occur, its appearance was noted usually at about the time that the separation of the dead soft tissues from the live tissues was nearing completion, i. e., about the end of the third week. Then a small incision through the crust or even the application of a dressing moistened with saline solution gave adequate drainage.

THE INTERMEDIATE PERIOD

In the series of cases reported here 93 thin grafts were applied to cover a granulating surface. These were applied on 59 patients at 80 separate operative procedures. The granulating areas covered averaged 89.6 sq. cm., and 32 of these were caused by a burn with an average area grafted of 93.6 sq. cm.

Relation of Area and Depth to Contractural Deformity.—The early recognition of not only the depth of epithelial destruction but the area of complete epithelial loss is an essential point that needs to be grasped by the surgeon if he is to develop a practical successful method of repair. In cases of burns of a degree (fig. 1) that destroy only a portion of the epithelial "pegs" within a period of from two to three weeks, reepithelization from below upward and skin grafting were seldom necessary. When all layers of the epithelium had been destroyed, the wounds tended to close by two methods: (1) by fibrosis and con-

7. Davidson, E. C., and Matthew, C. W.: Plasma Proteins in Cutaneous Burns, Arch. Surg. **15**:265-274 (Aug.) 1927.

8. Davidson, E. C.: The Prevention of the Toxemia of Burns: Treatment by Tannic Acid Solution, Am. J. Surg. **40**:114-116 (May) 1926; Sodium Chloride Metabolism in Cutaneous Burns and Its Possible Significance for a Rational Therapy, Arch. Surg. **13**:263-277 (Aug.) 1926; Tannic Acid in the Treatment of Burns, Surg., Gynec. & Obst. **41**:202-221, 1925. Glover, D. M.: Six Years of Tannic Acid Treatment of Burns, ibid. **54**:798-805, 1932. Harris, R. I., quoted by Davidson, E. C., and Penberthy, G. C.: Treatment of Burns in Children with Tannic Acid, Proc. Internat. Assemb. Inter-State Post-Grad. M. A., North America **5**:265-268, 1929. Herzfeld, G.: Treatment of Burns and Scalds by Tannic Acid, Practitioner **122**:106-111, 1929. Wilson, W. C.: The Tannic Acid Treatment of Burns, Medical Research Council, Special Report Series, no. 141, London, His Majesty's Stationery Office, 1929. Beekman, F.: Tannic Acid Treatment of Burns, Arch. Surg. **18**:803-806 (March) 1929. Bancroft, F. W., and Rogers, C. S.: Treatment of Cutaneous Burns, Ann. Surg. **84**:1-18, 1926; Arch. Surg. **16**:979-999 (May) 1928; New England J. Med. **202**:811-822, 1930.

traction of the granulating base and (2) by a slow scarred epithelization progressing centrally from the edges (fig. 2). The anatomy of the part very largely determined the tendency for the surface to close by the first or the second method. Thus, when the denuded area was over the side of the ribs or in the middle of the thigh, where the bony structures were strong and the soft tissues only moderately yielding, a greater part of the closure of a wound was made by the scarred epithelium, which, according to the natural rapidity of epithelial growth, grew in from the circumference. On the other hand, when the destruction of soft tissues was located in front or back of a joint which could be restricted in its normal radius of movement, the greater part of the

Fig. 1.—*A*, photograph of a rather superficial burn with fixative applied. In only one area (over the pubis) have all the layers of epithelium been destroyed. In a burn of this depth epithelization is quick because the new epithelium springs from the base. *B*, photograph of the same child taken three weeks after the burn.

wound closed by fibrosis, depending somewhat on whether the limiting scar was within or without the angle of movement. The larger the original surface destruction, the greater was the tendency to contracture and limitation of flexion or extension. In some instances an additional factor was added by the density and contractile pull of an innate tendency to the formation of a keloidal scar.

Preparation for Resurfacing.—By the end of the third week or the early part of the fourth week, when it was deemed that a well developed limiting wall of granulation tissue had formed, an abrupt change was made in the method of handling the local area. At this time the local burned area was wrapped within a wet thick gauze roll (fig. 3 *A*), which was reapplied twice daily and kept continuously wet. Early during this period, but not before, while the wound was being dressed

without anesthesia, gross dead tissues sometimes were cut away with scissors or a knife. When some difficulty or pain was experienced in removing the dressing, if the patient's condition permitted, the patient was placed in a tub bath (fig. 3*B*) for fifteen or twenty minutes until the dressings fell off more or less spontaneously.[9] Too long a period of immersion was found to be weakening in several instances,

Fig. 2.—*A*, photograph of a burn, which if allowed to scar over without aid will be forced by the underlying anatomy to close principally by epithelization from the circumference. *B*, photograph of a burn, which because of the anatomy of the region has closed principally by epithelization from the circumference. *C*, photograph of a burn which has closed principally by the contracture of the fibrotic base. *D*, photograph of a burn which over the ribs will close principally by epithelization from the circumference and in the axilla principally by contractural fibrosis.

9. Paulus of Aegina, 629 to 690 A.D. (cited by Pack, G. T., and Davis, A. H.: Burns: Types, Pathology and Management, Philadelphia, J. B. Lippincott Company, 1930) is said to be the first to use the continuous water bath. Passavant (Bemerkungen über Verbrennungen des menschlichen Körpers und deren Behandlung mit dem permanenten warmen Bade, Deutsche Klin. **10**:348, 365 and 373, 1858) first described and Hebra (Ueber continuirliche allgemeine Bäder und deren Anwendung bei Behandlung von Verbrennungen, Allg. Wien. med. Ztschr. **6**:331 and 359, 1861) popularized the use of a continuous wet dressing.

and if the patient was showing considerable constitutional reaction immersion was not deemed advisable. Immediately after immersion a wet gauze roll was wrapped about the denuded area.

Saline solution was usually used, but at other times a saturated solution of boric acid or of magnesium sulfate was used. The particular solution used, provided it was not toxic, was not considered of great importance. The advantages of wet dressings were judged to be promotion of drainage, maceration at the line of demarcation, mechanical aid to the separation of slough and possibly some mechanical stimulus to the formation of a proper bed of granulation tissue. Moreover, the

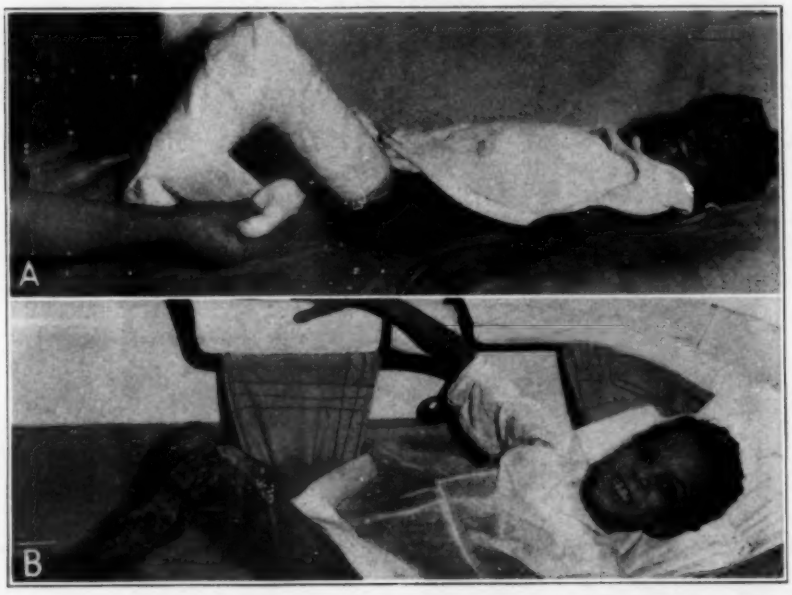

Fig. 3.—*A*, photograph of the method of applying a wet roller gauze roll to a wound when the time has arrived for separation of the dead tissues from the live soft tissues. Sufficient cotton pads are placed between the gauze to hold the moisture well. Externally a layer of rubber surrounds the gauze to prevent too rapid evaporation. Periodically the gauze is remoistened. The roll is changed morning and evening. *B*, if much pain is complained of when the roll is removed, if the condition of the patient permits he may be placed in a tub immersion for a few minutes and the gauze removed under water either by the patient himself or by the intern. The simplest solution to use is hypertonic saline solution. Any antiseptic solution, if nontoxic, will act the same.

cleanliness of the method and the repetition of the dressing twice daily were regarded of importance in shortening the period necessary to give a proper granulating bed. Besides the general condition of the patient, the most important aid to early epidermization from the circumference of the wound was cleanliness (fig. 4 *A* and *C*). In the consideration of

Fig. 4.—*A*, photograph of a large granulating wound of the leg of a patient ten days after beginning treatment by wet dressings and occasional tub immersion. She was burned thirty days before and was cared for at home by another physician, who used an ointment dressing which so far as the final result is concerned made little or no difference. An ointment dressing is, however, very "trying" on the patient and also on the one who has to do the dressing in the early days of the burn. A fixation method is a far more comfortable way of handling the situation. Whether or not it tends to prevent toxic absorption is quite another question. With the patient under gas anesthesia a large thin graft was applied from the opposite leg. Ninety per cent of the graft took. Thin grafts were taken from the inside of the left thigh, the outside of the right thigh and from the back. When taken along with the granulating area, owing to the burn such rather high percentage of body area was superficially denuded that about twelve hours after grafting skin from the inside of the right thigh, abdomen and back the patient showed signs of a mild "shock," which was interpreted as due to too wide an area of denudation (granulating area plus weeping area from which skin had been removed). A blood transfusion corrected this. *B*, photograph of the legs one year later. Extension and flexion were normal. *C*, photograph of a granulating wound three weeks after infliction of a burn from a clothes mangle. The tendons were destroyed. A wet dressing was used for one week before the photograph was made. Thin thick skin was grafted. *D*, photograph of the hand six months later. The patient obtained perfect flexion after the application of a thin graft to the granulating surface. Such a pleasant result does not often occur if the burn is of somewhat greater depth because of fibrosis of the tissues about the phalangeal joints.

the general condition of the patient, the factor of a relative secondary anemia was found to be important both as to the rapidity of epidermization and as an influence in obtaining a proper granulation bed on which a graft would "take." When the granulations were exuberant, a rather firm tight bandage aided in getting a firmer base. When evidence of anemia was present, a blood transfusion was given.

Grafting of Thin Skin on a Granulating Surface.[10]—The appearance of the granulating surface was used as the index to the time of grafting. The proper appearance was judged to be present when the surface was free from evidence of grayish slough or any gross pus and the granulation base was firm but not too exuberant or watery and was cherry red. Bacterial counts on smear were not considered of particular value. Anemic persons did not present granulation surfaces of the proper texture or color. Whenever grafting was attempted without the criteria being fulfilled, at least a part and usually most of the graft failed to "take." On the other hand, when it was present, practically in 100 per cent of the cases 90 per cent or more of the graft "took."

After laying the graft on the granulating surface, the same type of thick roller gauze dressing was applied as previous to grafting. This dressing was not changed for four or five days, and during this time it was kept saturated with saline solution or a saturated solution of boric acid. When the graft was located so that articular or muscular movement would probably cause it to slip, either stitches or a splint of some type or both were used so that fixation was definite.

A factor of particular interest to the surgeon is the reason for failure of a graft to "take." Of the 93 grafts applied to cover a granulating surface, in 42 there occurred a "take" of 90 per cent, which may be considered as practically perfect; in 13 there occurred a "take" of over 80 per cent, which may be considered as "good," and in 30 there occurred a "take" of over 70 per cent, which was usually sufficient so that further grafting to the granulating surface was not necessary. In 8 the loss ranged from 30 per cent to loss of the entire graft. The usual cause of loss was infection developing beneath a part or all of the graft. This usually was due to desultory preparation of the granu-

10. Possibly rather arbitrarily, a thin graft, to my mind, has been defined as any graft that leaves a part of the epithelial "pegs" in the area from which it was removed so that new skin regenerates from the bottom and the wound does not heal by growing in from the sides. Included in this definition would fall the "Thiersch" graft (Thiersch: Arch. f. klin. Chir. **17**:318, 1874) and the so-called "split" graft (Blair, V. P., and Brown, J. B.: The Use and Uses of Large Split Grafts of Intermediate Thickness, Surg., Gynec. & Obst. **49**:82-97, 1929) which is alleged to be a thicker graft than the Thiersch graft. At least the split graft places emphasis on the advantage of cutting a thick graft rather than a thin one.

lating surface, along with an error in judgment as to the time when the surface was in condition to receive a graft. In a few instances, improper fixation was the basic fault.

In patients on whom the skin was grafted when the hemoglobin content was below 65 per cent it was estimated that the chance of a

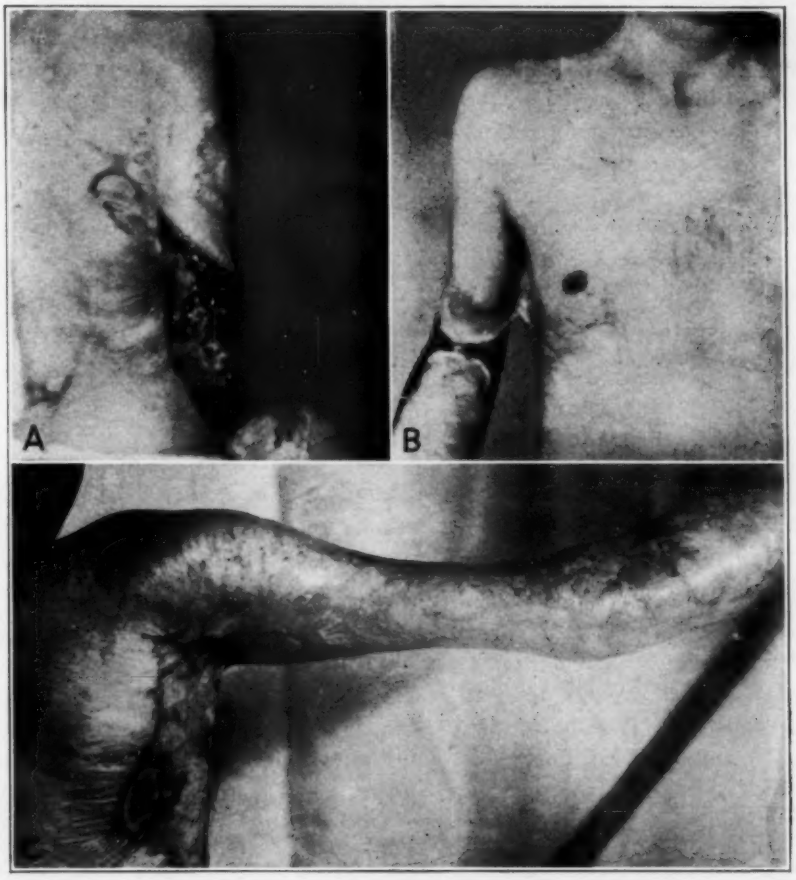

Fig. 5.—*A*, photograph of a granulating wound and cicatrix caused by an electrical burn inflicted eighteen months previously. The attachment of the triceps muscle to the olecranon had been destroyed. The patient could flex his arm by use of his biceps, and gravity caused extension. *B*, photograph of the front view of the healed cicatricial contracture of the axilla. *C*, photograph a few weeks after the application of a "split" graft to the axilla and to the granulating wound about the elbow. A little over 45 degrees of flexion was present.

successful "take" with a thin graft on granulating surface was decreased from one-third to one-half because of a greater tendency for the graft to be destroyed by infection.

When the granulating base was relatively new, a large thin graft showed a greater tendency to "take" well if the granulation tissue was not interfered with, but when sufficient fibrosis had occurred to give a firm scar base the chances of a complete "take" with a thin graft after the granulation and a part of the yellow scar base were sliced off were not decreased, and often some of the contracture was relieved, and better functional and cosmetic results were thereby obtained.

In several instances in which the patient was seen for the first time several months after the original injury and healed contractures had formed but part of the surface remained unhealed (fig. 5), it was often possible not only to cover the granulating area with a thin graft but to cross cut the contracture and largely correct the contractural deformity. In cases in which the contracture was graver, deformity was not always prevented, and the cosmetic result on such areas as the neck and face was often definitely unsatisfactory. Moreover, on such regions as the palm of the hand, the front of the leg and the bottom of the foot the amount of protection which a thin graft offered to the underlying tissues was not sufficient.

THE CORRECTION OF CICATRICAL AND COSMETIC DEFECTS AFTER COMPLETE HEALING

For the coverage of a fresh raw surface, I have used 165 thin grafts on 98 persons at 118 separate operations and 256 full thickness grafts [11] on 127 persons at 163 separate operations. Of the former grafts, 87, covering an average area of 29.5 sq. cm., were applied on 45 persons at 58 separate operations, and of the latter, 155, covering an average of 26.4 sq. cm., were applied on 67 persons at 91 separate operations to correct a healed cicatrix following a burn.

Chance of Failure of Graft to "Take."—Fortunately one seldom has to contend with the chance of not getting a good "take" when using a thick skin graft for the correction of a healed defect. When a full thickness graft is used to correct a healed defect, unfortunately one has to consider the possibility of a partial or even a complete failure to obtain a good "take." Of the 155 full thickness skin grafts used to correct the damage resulting from a burn, 130 showed (from 95 to 100 per cent) good "takes," which meant that a surgically clean surface was obtained, that the hemostasis was adequate, that the proper tension of transplanted skin was obtained, that the proper pressure was applied

11. A full thickness skin graft (Wolfe, J. R.: New Method of Performing Plastic Operations, Brit. M. J. **1**:360, 1875) is a free transplant which usually leaves no part of the epithelial "pegs" in the area from which it is removed. Section is made across the lower third of the corium. Unless the resulting wound is drawn together by sutures, the defect closes by a combination of fibrotic contracture and scarred epithelization.

to gain coaptation between the graft and the bed and that adequate fixation or splinting was provided. In 3 instances the whole graft was lost. In 25 instances the loss was partial and ranged from 10 to 90 per cent. The causes of the loss were judged to be infection of all or of some part of the grafted area in 12 cases, lack of adequate pressure in 12, too much pressure in 1, blood clot in 2 and improper splinting which allowed muscular movement beneath the graft in 1.

Average Final Contracture of the Grafted Area.—Provided a good "take" occurred, the most important influence on functional result was the final amount of contracture of the grafted area. The subsequent average contracture of the full thickness skin graft when used in the correction of the damage resulting from a burn averaged 17 per cent and of the thin graft, 38 per cent.

Dressing for Grafts on Fresh Raw Surfaces.—As a rule, a graft applied to a clean raw surface was fixed by stitches, whether or not a thin or thick graft was used, a dressing of gauze treated with 5 per cent bismuth tribromphenate in petrolatum was laid on the graft and then a moderately thin layer of gauze was applied. Finally, a damp marine sponge was compressed by a bandage or stitches or both over the graft (fig. 6 *A* and *B*).

When movement seemed an eminent factor, some type of fixation by splinting was added. Externally, when the anatomy of the location was such that an outlay wax stent (fig. 6 *C*, *D* and *E*) gave better chances of the proper amount of pressure and tension on the graft, the tissue to be grafted was stitched about a wax form. Internally, within the mouth, as a rule, a wax stent was used.

The Selection of the Type of Graft.—My judgment as to the better type of graft to apply to a given region [12] under a certain group of circumstances has undergone considerable revision from time to time. Usually the ideal objective was balanced against the probability or the possibility of attainment in a reasonable manner.

When one wishes to correct a contracture about such a region as the axilla, the popliteal space or the elbow, full movement of the extremity is the first consideration. In the axilla it was found that a good "take" with a full thickness skin graft is somewhat difficult to obtain because of the likelihood of not getting uniform pressure. One does not encounter this difficulty about the elbow or the popliteal space. A proper amount of a thin graft will usually correct an axillary contracture (fig. 7 *A* and *B*). As this graft is the most certain to grow and the postoperative period of dressing is short, after making use of

12. Padgett, Earl C.: Full Thickness Skin Grafts in the Correction of Soft Tissue Deformities, J. A. M. A. **98**:18-23 (Jan. 2) 1932; Early and Late Treatment of Burns, J. Kansas M. Soc. **34**:184-188, 1933.

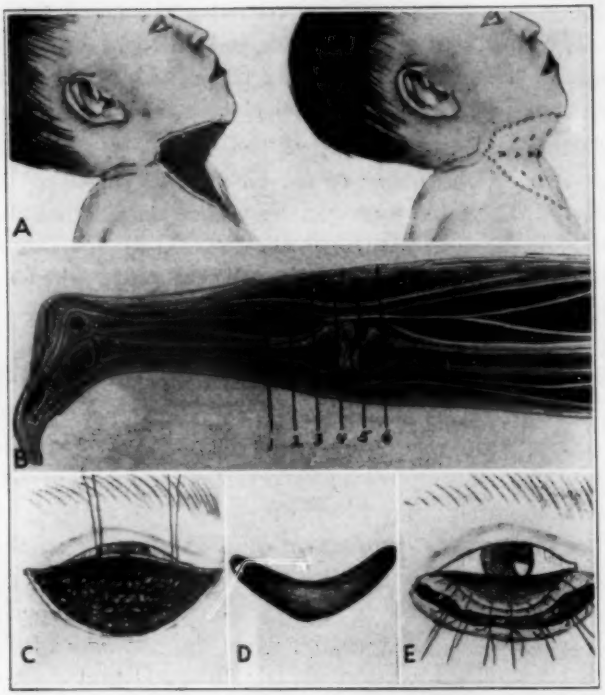

Fig. 6.—*A*, diagram of the method of cross-cutting a contracture and getting overcorrection. In this diagram a full thickness graft is shown stitched in place. In the gutter a few stitches were placed to aid in fixation. A few stab holes were made to prevent accumulation of fluid beneath the graft. When a thin graft was used the stitching was similar but looser, and the graft was made to overlap the edge of the skin. When more than one graft was used to cover the raw area, the grafts were overlapped and stitched through and through to the base beneath. *B*, diagram to illustrate the layers of the dressing: *1*, the graft; *2*, layer of bandage gauze impregnated with 5 per cent bismuth tribromphenate in petrolatum; *3*, thin layer of wet gauze; *4*, thick overlapping layer of marine sponge; *5*, moist cotton pad and firm bandage; *6*, possibly some type of splint to prevent movement. In this case an external cast was used. Often no splint is necessary. Whether a splint is needed for fixation depends on the location. *C*, diagram of an ectropion of the lower eyelid caused by a cicatrix which has been corrected by a lengthwise incision just beneath the eyelashes and cross-cutting of the cicatricial bands. *D*, diagram of a stent made of dental modeling composition before insertion over the muscle of the lower eyelid. *E*, diagram showing a method of wrapping a thick thin graft or a thin full thickness graft about the wax stent; by means of interrupted silk stitches pulled snugly over the stent the graft has been placed on tension and pressure given so that firm contact with the raw base is obtained. From 30 to 50 per cent overcorrection is made to allow for subsequent contracture.

any material available for a switch pedicled flap, a thin graft was usually used for the remainder of the raw surface in the axilla. The same was applied to perineal contractures. About the elbow and about the popliteal space, groin or back of the hand both types of grafts have been used, but because of the lesser tendency to contracture the full thickness graft was more often given the preference (fig. 8 *A* and *B*).

In cicatricial contracture of the palm of the hand (fig. 8 *C*, *D* and *E*) and the flexor surfaces of the fingers, the full thickness skin graft offered on the average a good functional result. Although a good

Fig. 7.—*A*, photograph of a healed cicatricial contracture of the left axilla, neck and thumb. *B*, a so-called "split" graft (a thick thin graft) was used for correction of the axillary contracture after cross-cutting the contracture. The photograph was made six weeks after the patient left the hospital. He was seen six months later, and the correction was complete. A full thickness graft was applied over the left thumb contracture. *C*, photograph of a neck contracture. The contracture was cross-cut, and a full thickness graft from the thigh was applied. As the patient was a boy and a collar would be worn it was considered that the essential factor was functional correction. *D*, lateral view of the neck six weeks later.

"take" was more certain and the subsequent period of dressing was shorter, the thin grafts on the ventral surface of the fingers (fig. 9) between the fingers and over the dorsum of the hand usually did not give as satisfactory a result as did the thicker graft. The final contracture was greater, the appearance was not so near that of normal skin and in the case of ventral surface of the fingers the protection

was not always adequate. The full thickness skin graft in the palm of the hand gave a good result functionally and cosmetically. The ultimate contracture was not so great that it could not be compensated for at the time of the operation, and the protection was adequate. After a graft was applied, some type of splint to hold the fingers of the hand in a position of overcorrection for several weeks aided the result very materially.

On the anterior portion of the neck a thin skin graft, although almost certain to "take," usually contracted from 50 to 70 per cent, too greatly to correct the contracture, and the appearance usually was not

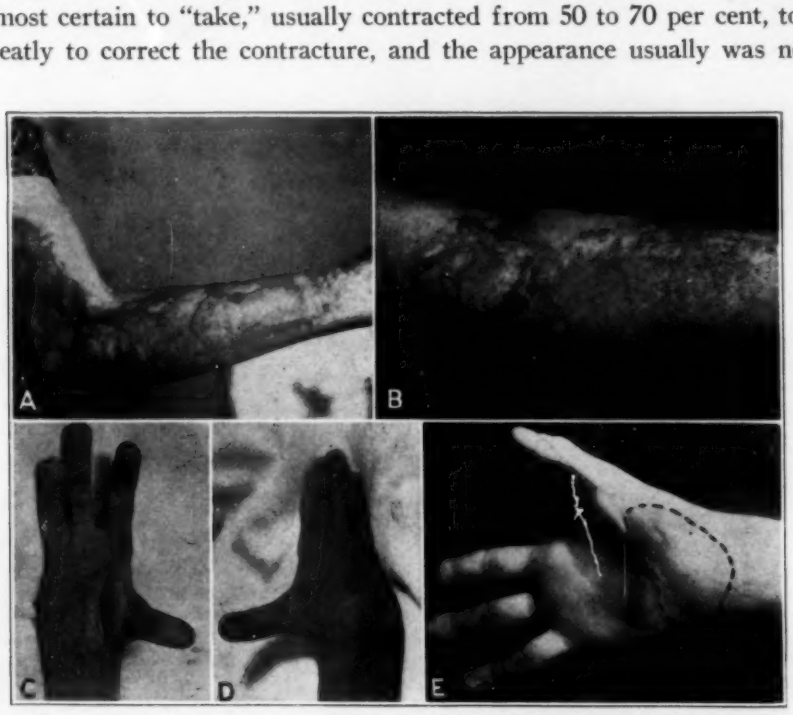

Fig. 8.—*A*, photograph of a contracture of the region of the elbow. *B*, photograph made two months after release of the contracture and application of a full thickness skin graft. *C*, photograph of a contracture of the palm of the hand, palmar view. *D*, dorsal view of the hand. The little finger was removed at some previous operation. The contracture was cross-cut, and a full thickness skin graft was applied. *E*, photograph of the preceding hand eight months later. The graft lies within the dotted line.

satisfactory. In over 80 per cent of the attempts a good "take" after the application of a full thickness skin graft to the upper and anterior portion of the neck was obtained. When this occurred the contracture was corrected in from one to two operations, and the cosmetic result was good. The swallowing movement usually caused some loss of a

graft over the thyroid cartilage no matter what type of dressing was used with the idea of preventing it. In later cases an attempt was always made not to leave a raw area over this region.

After both thin and full thickness grafts had been tried out over the thyroid cartilage, the adjacent sides of the cheek and the mandible, it was found that the latter usually was given the preference, because the full thickness graft more nearly approximated the normal skin in appearance (figs. 10, 11 *A* and *B* and 12). On the sides of the face the full thickness graft has been given a decided preference. In these regions the final result after a satisfactory "take" of a full thickness graft justified the risk of not getting a good "take." Some of the most

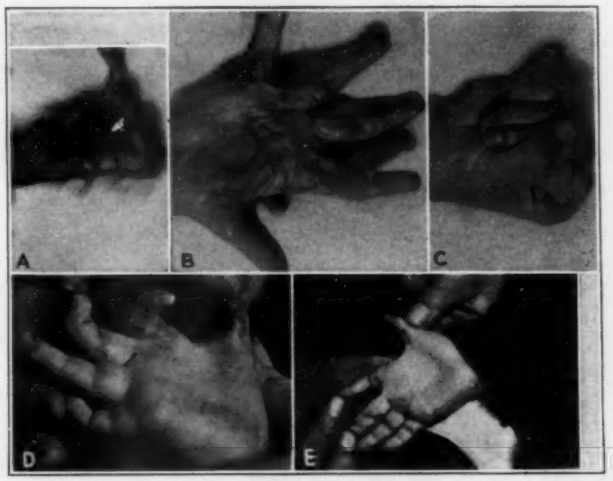

Fig. 9.—*A*, photograph of a ventral cicatricial contracture of the fingers of the right hand. The scar was cross-cut, and a full thickness skin graft was applied. *B*, a photograph three months later showing extension. *C*, made at the same time, shows flexion. *D*, contracture of the thumb and first finger. The contracture was cross-cut, and a full thickness skin graft was applied. *E*, a photograph made three months later.

brilliant results were obtained with large full thickness grafts to the face. Although in several instances the appearance of the graft was somewhat whiter than normal skin, a thick thin graft gave a satisfactory result when applied over the orbicularis oris muscle for an ectropion of the upper or the lower lip.

When a full thickness skin graft was used on the neck and chin, about the mouth and over the cheek, in at least half of the cases a secondary operation was found to be necessary after a period of several months, for the purpose of excising the rather heavy scar which often

forms at the juncture of a full thickness skin graft with the surrounding normal skin. Moreover, even in advent of obtaining a good "take" of a full thickness skin graft on the face, the possibility had to be considered of having the graft appear too shiny or in brunettes of presenting a discoloration from pigmentation. Although there was a tendency for the full thickness graft to have a slightly shiny appearance, most of the grafts that "took" well without much superficial exfoliation eventually showed grossly almost the normal texture of the skin of the region from which the graft was removed. Those grafts in which

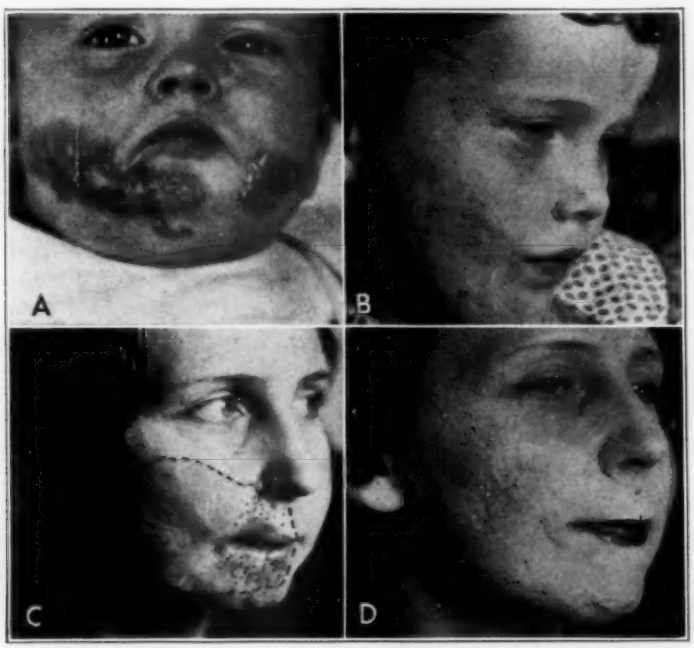

Fig. 10.—*A*, photograph of a cicatricial keloidal contracture of the side of the face. The scar was removed, and a full thickness skin graft was applied. *B*, a photograph made two years later. *C*, photograph of a scar of two thirds of the side of the face and extropion of the upper and the lower lid. A full thickness skin graft was applied to the side of the face. The dotted outline shows the extent of the scar. Over the dotted area on the region of the upper and the lower lip a heavy split graft was used. *D*, photograph of the final result two years later after excision of surrounding scar.

some superficial exfoliation occurred had more of a tendency to show pigmentary changes. In pronounced brunettes, pigmentation sometimes occurred in a perfect "take."

On the sides of the neck, over the sternocleidomastoid muscle and the posterior portion of the neck a thin graft was found to give

an acceptable result functionally and cosmetically. Here the contracture was usually less than one-third. Because of the ease of application and the certainty of a "take" in this region, the thin graft was given preference.

When a muscle was near the surface, as about the eyelids (fig. 11, *C* and *D*), about the lips or over the sternocleidomastoid muscles on the side of the neck, the results obtained after the application of a thin graft were as good or in rare instances even better than that after obtaining a good "take" with a full thickness graft. When such is the case, the greater likelihood of a perfect "take" after the application of

Fig. 11.—*A*, a photograph of a large hemangioma of the face which had been burned by the x-rays and radium. The area showed telangiectasis and mottled and scaly patches. Complete removal was carried out, and a large full thickness skin graft was applied. *B*, a photograph of the result one year later. *C*, a photograph of ectropion of the lower eyelid with destruction of the outer canthal region. The scarred side of the face is shown by the dotted outline. After excision of the whole scar, a large heavy split graft was applied to the temporal region and the side of the face and a thick thin stent graft was used over the eyelids. *D*, a photograph of the result two years later.

a thin graft, the shorter period for postoperative dressing and the probability of only a slight cicatrix at the junction of the graft with the normal skin speak strongly in favor of the thinner graft. For this reason about the eyelids most often a relatively thick thin graft draped about a wax form was used, but more rarely a thin full thickness graft

from back of the ear was used. Probably the latter method most nearly approached the ideal about the eyelids.

Acceptable eyebrows were made with a full thickness graft from the scalp. The hair was found to be somewhat sparse and less plentiful than in a normal scalp, but with care in clipping the new eyebrow was fairly successful.

Fig. 12.—*A*, a photograph of a severe burn with a partially healed cicatrix. Multiple skin grafting operations were carried out after the contracture was cross-cut, which was to be corrected at the given operation. Note the contracture of the neck, about the lower lip and axilla and over the groin. The right thigh was pulled into a position of nearly 45 degrees flexion. The boy lay in bed in an almost vertical ball. A "split" graft was used for the axilla and the right groin. Full thickness grafts were used for the neck and chin, beneath the lower lip and behind the right ear to release it from his head. *B*, a photograph of the general result eighteen months later.

THE PRACTICABILITY OF HOMOGRAFTING

In 1932 I published my results with 44 experimental isoskin grafts, or homografts.[13] Since that time the experiment has been repeated in

13. Padgett, Earl C.: Is Skin Grafting with Isografts or Homografts Practicable, West. J. Surg. **41**:205-212, 1932; Is Skin Grafting with Isografts or Homografts Practicable? Surg., Gynec. & Obst. **25**:786-787, 1932.

6 cases. My data show that the result to be expected after isodermic transplantation by ordinary methods, at least, may be summarized as follows: An immediate "take" occurs in the majority of cases. In nonrelated persons, between the second and the third week the grafts begin to disappear, and by the end of the fourth week they have completely disappeared. In persons related by blood (syngenesiotransplantation), such as father and son or even uncle and nephew, the grafts "take" and remain viable about three weeks, but by the end of the fifth week they are destroyed. In identical twin transplantations (the closest possible syngenesiotransplantation or "near relation transplantation") the grafts may remain. Syngenesiotransplantation of skin is theoretically improbable except in identical twins, in whom it is theoretically probable and clinically has occurred. The failure of experimental isodermal grafts on man and on animals to remain viable or to show a relationship to the blood group in the length of time viability is present and theoretical reasoning argue against the blood group of the patient as playing a rôle of any essential significance in homotransplantation of the skin. The bulk of experimental and clinical experience is in agreement that isotransplantation or homotransplantation of skin is not practicable except possibly in identical twins. Thus, some antagonism not as yet understood apparently exists between the cells of the host and the donor, even in close relatives, and as the distance of the relationship within the species is increased progressively the antagonism is more marked. Moreover, without species the antagonism is even more marked than within species. The great importance of the relative nearness of the relationship of the genes of the host and the donor of the transplant is apparently the crux of the matter.

SUMMARY

Of a series of 514 skin grafts transplanted at 361 separate operations on 257 different persons, 299 were transplanted at 193 separate operations on 144 persons to alleviate a burn.

To exemplify the problems encountered in the care of a severe burn in the early, the intermediate and the late stage, a series of 144 burned persons was found to present the necessary situations.

In the care of the severely burned greater emphasis should be focused early on alleviation of the profound systemic disturbance than is placed on the care of the local lesion.

The recognition of the depth and the area of complete epithelial destruction is an essential point to be grasped if one is to understand the principles of reepidermization and the basic cause of contractural deformity.

Early resurfacing after a large complete loss of skin should always be the goal of the efficient surgeon because of the decrease in the

period of convalescence with its economic potentialities and the prevention of contractures with the functional incapacitation which accompanies them.

Provided the general condition of the patient is good, one's success in growing thin skin grafts on a granulating surface is directly proportional to the general cleanliness of the surface.

In an anemic person the chance of a good "take" on a surface of granulation tissue is decreased.

In the successful grafting of skin dependence on simple fundamental principles and methods, in contradistinction to a special type of graft with or without a "far-fetched" method of placement or puncturing or dressing, is important.

In the correction of cicatricial defects after complete healing has occurred, the decision whether to use a thin graft or a full thickness graft depends on a careful balancing of the characteristics of the two grafts, the main object to be attained in a given region and the relative risk of failure to get a good "take." Sometimes the disability entailed in the removal of the graft and the length of the period of postoperative dressing also become factors to be considered.

After observing a series of 50 experimental homotransplants in man, the conclusion was reached that isodermal grafting is not a practicable procedure unless an identical twin is available.

ABSTRACT OF DISCUSSION

Dr. G. B. New, Rochester, Minn.: As Dr. Padgett has brought out, the treatment of extensive burns should always be considered an emergency of the greatest importance. To obtain the best results, treatment should be directed as soon as possible by the combined efforts of a team consisting of an internist, a biochemist and a surgeon.

In a recent symposium, Osterberg showed that the clinical picture observed in cases of extensive burns is due to excessive concentration of the blood with its resultant phenomenon and not to specific toxins produced as a result of the burning of the tissues. Bannick and Keith emphasized the necessity in cases of extensive burns of early relief from pain by the administration of morphine in order to prevent shock and of relief from marked dehydration. They urged that fluids be replaced early by sodium chloride and dextrose solutions.

The surgeon must cover the raw surfaces with a tannic acid spray as soon as possible. Seeger, however, has shown that there is no reduction in the ultimate mortality which can be attributed to the use of tannic acid, other factors in the treatment being comparable. The mortality has been reduced in the first five days, many of the patients dying, however, in the later stages. Of 369 cases of burns in the Milwaukee Children's Hospital, 39, or approximately 11 per cent, were fatal; of 197 cases in which tannic acid was used, 23, or 12 per cent, were fatal; of 172 cases in which other methods of treatment were used, 16, or 9 per cent, were fatal.

Brown and Blair's excellent work on the use of baths of hypotonic saline solution and early covering the raw areas with shaved skin grafts has been one of the most striking advances that I have seen in the treatment of burns. The

type of skin grafting employed must depend on the usual factors in determining the use of skin grafts in general. When the granulated area is ready for grafting, a shaved graft will cover the area with a high percentage of "takes," but when such a graft is used about the face and neck, there is usually a great deal of contraction, and the color is frequently not satisfactory. A secondary free full thickness skin graft or a skin flap becomes necessary. When a full thickness skin graft is used about the cheeks, submental or submaxillary region, wiring the upper and the lower teeth together as one would in a fracture of the lower jaw, the patient being fed with a Rehfuss tube, prevents any movement, thus adding considerably to the percentage of "takes." A free full thickness skin graft is best used over the muscles of expression, as it is almost impossible to get a flap thin enough so that the muscles show through. The color, of course, in the flap is much more satisfactory than can be obtained by a shaved or free skin graft. A large tube flap taken from the chest with one pedicle in the infraclavicular region and the other well down on the chest gives excellent results. The area in the infraclavicular region simulates closely the skin of the face and neck in color and texture and makes ideal material for this purpose. The lower end of the tube flap on the chest is carried to the neck or region of the mastoid, and then the skin in the infraclavicular region is carried to the neck or face where it is to be utilized. If the full thickness of the nose or cheek has been destroyed, it is necessary to line the area in the infraclavicular region with a full thickness skin graft in order to prevent the transferred skin from pillowing. In the cases with scarred band contractures, the use of the Z or VY incision operation will release them and correct much of the deformity. Dr. Padgett's results in this work have been extremely good, and he should be highly complimented.

Dr. James Barrett Brown, St. Louis: Although there are many reports on the treatment of burns, the small number of authors who publish final results as to healing and function in large series of patients who have lost the full thickness of the skin over a wide area is small. The late care and repair in such cases may require more time-consuming and exacting work than the primary treatment.

When deep burns heal there are contractions of the surrounding tissue and final closure of the defect by "scar" epithelium growing in from the sides. This scar epithelium is thin, contains no hair or sweat glands and lies flat on fibrous scar tissue that has no papillary layer or other semblance of normal derma. This condition does not change throughout years except that there may be some softening. There may be a general shortness of the skin necessary for function; over weight-bearing areas there may be chronic ulceration, and in any area this thin scar epithelium is subject to rapid and wide loss from infection or trauma. Microscopic studies of a large number of scars have shown this plainly, and on several occasions I have taken specimens for biopsy from areas that have been traumatized and have found the entire "scar" epithelium grossly dissected loose from the underlying fibrous tissue by hemorrhage.

The substance of the care of areas in which there is an extensive loss of the surface is that they should be repaired as soon as possible with skin grafts. The main difference in my method of repair in such cases from that discussed by Dr. Padgett is that I limit the number of full thickness skin grafts and substitute a graft that includes from one third to three fourths of the thickness of the derma. This graft might be called a thick Ollier-Thiersch graft, but the term thick split graft may be used to identify it from the thin, almost useless Ollier-Thiersch graft and from the full thickness graft.

The thick split graft may be cut rapidly and easily in large pieces and will "take" almost as successfully as the thin Ollier-Thiersch graft. It does not give

as good immediate result as the full thickness graft, but it may be risked on open wounds, and perhaps its greatest advantage is that healing of the site from which the graft is taken occurs rapidly, in contradistinction to the great trouble experienced in getting the sites from which large full thickness grafts are taken to heal. I have grafted 173 square inches of this type of graft at one time. Healing progresses toward the surface from the deep glands in the derma, and microscopic studies have shown complete surface coverage as early as the sixth day. This process is a "dedifferentiation" of the epithelial cells and progresses in the opposite direction of the growth of a cancer. A semblance of the picture of actual cancer may occasionally be seen in examination of this surface healing process in different stages.

One of the main uses of this type of graft is in effecting major repairs with a minimum of time and operations. The repair of badly contracted axillary and popliteal regions seldom requires a full thickness graft or pedicle flap, and, at least for the primary release of contractures about the neck, the thick split graft may be used to get the head up and the mouth closed and to allow the patient to resume a normal social and economic status. Then, if there is too much roughness or recurrent deformity, any other method of repair may be used.

Dr. Earl C. Padgett, Kansas City, Mo.: Possibly I have favored the full thickness skin graft a trifle more than is necessary. A certain amount of idealism has entered into the matter. When a good "take" of the full thickness graft is obtained, it undoubtedly in certain instances has qualities superior to those of any other graft. This is true especially for the face and neck. It would seem that with the use of a procedure with which one can succeed completely in 80 per cent of the attempts and can obtain partial success in another 15 per cent of trials, if a little more could be learned of the reasons for failure and certain adverse factors eliminated, one should succeed in nearly 100 per cent of the trials. I have succeeded in obtaining a good "take" in 5 cases of hemangioma of about one half of the face. Such an operation is heroic, but in adults I believe that it gives a result when successful which cannot be approached by other methods. An occasional failure in growing a full thickness skin graft, however, must be expected. I have had a failure after excising a large cicatrix of the face following a burn. The principles that make for success are the same, however, after excision of either lesion—a cicatrix or a hemangioma.

SURGICAL DISEASE OF THE GALLBLADDER

CLINICAL AND PATHOLOGIC REVIEW OF THE DISEASE IN 133 PATIENTS OPERATED ON AT THE MOUNT SINAI HOSPITAL, WITH FOLLOW-UP STUDIES

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The incidence of disease of the gallbladder in the adult population, the term being limited to include calculous and noncalculous cholecystitis, is very high. Stewart, of the University of Leeds, is quoted by Blackford, King and Sherwood (cited by Palmer [1]) as reporting evidence of disease of the gallbladder in 16.4 per cent of 6,000 routine autopsies. Blackford and his associates concluded that more than half of the adults past 30 years of age have abnormal gallbladders and that approximately one fifth of these have gallstones. According to the statistical studies of Graham and his co-workers (cited by Hauser [2]), from 20 to 25 per cent of all adults have gallstones and probably an equal number have cholecystitis without stones. Thus, about 40 per cent of the adult population have disorders of the biliary system, which in probably the majority of instances are at times associated with more or less severe symptoms. McEvedy [3] found that calculi are absent in 20 per cent of persons with definite cholecystitis, whereas in a small percentage of patients with gallstones the gallbladder shows no definite change or evidence that the inflammation has followed the calculi. Moynihan (cited by Burton [4]) said that "all gall-stones except pure cholesterin calculi invariably cause symptoms."

From the Laboratories and Surgical Departments of the Mount Sinai Hospital.

1. Palmer, W. L.: Gall Bladder Disease: Remarks on Symptoms, Diagnosis, and Treatment, Internat. Clin. **1**:111-123 (March) 1935.

2. Hauser, H.: Practical Application of Cholecystography, Radiology **21**: 472-477 (Nov.) 1933.

3. McEvedy, P. J.: Gall Stones and Cholecystitis, Clin. J. **64**:111-115 (March) 1935.

4. Burton, J. A. G.: Cholelithiasis: A Summary, Glasgow M. J. **121**:14-23 (Jan.) 1934.

Although the literature is replete with clinical reports and follow-up studies of cases of disease of the gallbladder, there have been few studies dealing with the relationship between the pathologic changes found at operation, the results of the histologic study of operative specimens and the clinical course in any particular series of cases of this disease. In the present study it has been our purpose to correlate the histologic structure and the gross pathologic picture of the gallbladder found or removed at operation with the clinical symptomatology and the subsequent results of operative treatment in those cases in which follow-up studies were possible. With this in view, we have made a complete and careful study of 133 patients with disease of the gallbladder who were treated at the Mount Sinai Hospital from 1930 to 1935. Follow-up data were obtained in 61.6 per cent of the group. Patients with malignant growths of the biliary tract or persons who were not operated on were not included. The results thus obtained have been critically correlated with the histopathologic picture. Coincidentally, an attempt has been made to analyze the causes of morbidity and mortality with the purpose of recognizing pathologic conditions corresponding to the clinical course.

The controversy over the advantages of cholecystostomy as compared with cholecystectomy seems at present to have abated, but it is by no means conclusively settled. Surgeons now agree that an infected gallbladder is incapable of being restored to normal function (Graham [5]) and may also act as a focus of infection. Moreover, the degree of disability which a patient suffers as the result of a diseased gallbladder is dependent not only on the changed content of the gallbladder and the involvement of its wall but on the associated involvement, for which the diseased gallbladder may be in part responsible, of the pericholecystic structures, i. e., the liver, pancreas, duodenum and common bile duct.[6]

Hartmann, Alvarez, Deaver, Zinc and others (cited by Mackey [7]) concluded from their findings that the results of cholecystectomy in cases of cholecystitis without stones are better than the results in cases of frank cholelithiasis. They explained their findings by the assumption that cholecystitis without stones represents the earliest stage of disease of the gallbladder and expressed the belief that when the stage of cholelithiasis has been reached there have developed, in a large proportion of cases, lesions in other viscera, which persist after cholecystectomy

5. Graham, R. R.: Surgical Therapy in Gall Bladder Disease, Canad. M. A. J. **30**:119-123 (Feb.) 1934.

6. Deaver, J. B.: Causes of Morbidity and Mortality of Operation for Gall Stone Disease, Surg., Gynec. & Obst. **49**:308-315 (Sept.) 1929. Graham.[5]

7. Mackey, W. A.: Cholecystitis Without Stone: Investigation of Two Hundred and Sixty-Four Operated Cases from the Clinical, Radiological, and Pathological Aspects, Brit. J. Surg. **22**:274-295 (Oct.) 1934.

and continue to cause symptoms. On the other hand, Flörcken, Gundermann, Seuleberger, Hitzrot and Cornell, Müller, Lahey and others (cited by Mackey[7]) found that the clinical results of cholecystectomy were better in cases of cholelithiasis. In many cases in which the stoneless gallbladder was removed at operation but symptoms have persisted, they argued that the gallbladders have not been the cause of the symptoms with which they have been libeled. On the basis of a statistical study, Peterson[8] stated that favorable results were obtained with cholecystectomy in cases of cholecystitis associated with stones, i. e., cure in 83 per cent, while in cases of cholecystitis without stones the operation resulted in cure in only 52 per cent. Cholecystostomy alone in cases of each type resulted in a cure in 52 per cent. Mackey,[7] after reviewing 6,000 cases reported in the literature, summed up the evidence obtained as follows: "The experience of a large number of surgeons in the past has shown that cure or improvement after cholecystectomy may be expected in nearly 90 per cent of cases of cholelithiasis and in nearly 80 per cent of cases of cholecystitis without stones." Others like Judd and Priestley and Hueck (cited by Mackey[7]) could find no appreciable differences in the results following operation in these two types of cases.

In our group of patients there were 15 with cholecystitis without stone formation who came to operation. Of this number, follow-up information was obtained on 7. Mackey,[7] in a similar study, found that the results were usually more gratifying in cases in which the clinical symptoms were well marked than in those in which the symptoms were not marked. It appears also that the removal of those gallbladders which presented definite pathologic changes yielded better clinical results than excision of gallbladders in which the pathologic changes were minimal.

Since our group of patients with noncalculous cholecystitis is small and the results obtained by study were in agreement with those reported by Mackey,[7] we have made a composite table of the data in each group, which illustrates the findings discussed very clearly.

Of our series of 118 patients with cholecystitis with stone formation, 110 were treated by cholecystectomy; of these, 6 died after operation (table 2). The remaining 8 were treated by cholecystostomy, and of these, 3 died. The high mortality (37.5 per cent) after cholecystostomy may be explained by the fact that this type of operation is employed at the Mount Sinai Hospital only on patients whose general condition precludes the employment of any drastic form of surgical intervention.

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8. Peterson, T.: Gall Bladder Disease: A Critical Clinical Study, Minnesota Med. **18**:123-127 (Feb.) 1935.

Lipshutz,[9] in a recent study, concluded that the operative mortality in cases of acute cholecystitis is less when operation is performed as soon as the patient has been adequately prepared with dextrose and fluids than when operation is deferred. Mentzer,[10] in a study of 43 cases of acute cholecystitis, found that what appears to be a mild or moderately severe cholecystic inflammation clinically may actually be a fulminant cholecystitis. Mentzer, Kirschner and Nordmann (cited by Bashein [11]) and many other surgeons advocate early operative intervention, usually cholecystectomy, in cases of acute cholecystitis. The findings in our present study are in accordance with this point of view. Twenty-two patients with acute cholecystitis associated with stones were treated by cholecystectomy, with 1 death, a mortality of 4.5 per cent. Seven patients with acute cholecystitis were treated by cholecystostomy, with 2 deaths, a mortality of 28.5 per cent.

TABLE 1.—*Correlation of Pathologic Changes, Clinical Symptoms and End-Results in 147 Cases of Cholecystitis Without Stones*

		Results in Cases With History of Biliary Colic (52)			Results in Cases Without History of Biliary Colic (95)		
	Pathologic Lesion Present	Well	Improved	Unimproved	Well	Improved	Unimproved
Mackey's cases	Minimal lesion	2	6	7	9	15	15
	Cholesterosis	8	0	5	6	2	11
	Chronic catarrhal cholecystitis	10	6	1	7	12	13
	Chronic fibrous cholecystitis	1	1	0	1	2	0
Authors' cases	Chronic fibrous cholecystitis	2	3	0	0	0	2
	Total of both groups	23	16	13	23	31	41

The average period of preparation for the patients with acute cholecystitis who were subjected to cholecystectomy ranged from two and four-tenths to three and six-tenths days (table 2). The average period of convalescence of these patients with acute gangrenous calculous cholecystitis and acute exacerbation of a chronic calculous cholecystitis was thirteen and a half days. Three patients with acute ulcerative calculous cholecystitis had an average convalescence of eighteen and three-tenths days. The average period of preoperative hospitalization for the 88 patients with subchronic and chronic cholecystitis was about nine days, as compared with the average of three days for those with acute cholecystitis. This is explained by the fact that many of the

9. Lipshutz, B.: Acute Cholecystitis, Ann. Surg. **101**:902-911 (March) 1935.

10. Mentzer, S. H.: Acute Gall Bladder Manifesting Few Signs or Symptoms, Surg., Gynec. & Obst. **55**:709-716 (Dec.) 1932.

11. Bashein, H.: Gall Bladder Surgery: Observations from Series of Cases as to Advantages of Early Operations, Am. J. Surg. **23**:506-513 (March) 1934.

patients in the first two groups were usually admitted to the medical services for complete study before being subjected to operation.

We were able to obtain follow-up data on 17 of the 29 patients with acute cholecystitis who were operated on. All 17 were either completely cured or else greatly improved. This finding is in sharp contrast to the results obtained by cholecystectomy in cases of non-calculous cholecystitis, as shown in table 1; in a series of 147 patients, 56, or 38 per cent, failed to be relieved or were made worse by the operation.

Of the 88 patients with subchronic or chronic cholecystitis with stone who were treated by cholecystectomy, 6, or 6.8 per cent, died after operation. Of the remaining 82, we were able to obtain follow-up data on 50. In this group 28 regarded themselves as cured, and 21 stated that they were greatly improved, suffering only from occasional attacks of dyspepsia after dietary indiscretions. Only 1 patient in this group was found to be unimproved. Thus, of the group of 104 patients with calculous cholecystitis who survived cholecystectomy, we were able to obtain follow-up data on 63. Of these, 62, or approximately 98 per cent, were either cured or greatly improved, while only 1 patient showed no improvement.

Statistical and follow-up data in the recent literature on cases of disease of the gallbladder [12] are in overwhelming agreement as to the most important criteria for establishing a diagnosis of such a condition.

1. A typical history, which includes intermittent pain in the right upper abdominal quadrant, with or without jaundice, and a persistent gaseous indigestion characterized by a qualitative dyspepsia for fried and fatty foods, is an important indication. According to Stanton,[12a] if a surgeon is definitely certain of his ground relative to the clinical history of biliary colic, he can proceed to remove the gallbladder even if there is no obvious recognizable pathologic process present at the operative table.

Table 3 shows that colic, which was present in 112 of 118 cases of various types of cholecystitis, is the most constant clinical symptom and substantiates what Stanton has said about the significance of biliary colic. Additional justification for the removal of the gallbladder in these cases may be found in the fact that of the 63 patients on whom a follow-up study was made, 62 were either cured or greatly improved.

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12. (*a*) Stanton, E. M.: Stoneless Gall Bladder: Study of Operative Cases, Am. J. Surg. **18**:246-250 (Nov.) 1932. (*b*) Hitzrot, L. H.: Correlation of Other Diagnostic Procedures with Cholecystography in Two Hundred and Fifty Cases of Suspected Gall Bladder Disease, Am. J. M. Sc. **186**:203-213 (Aug.) 1933. Mackey.[7]

TABLE 2.—*Correlation of Pathologic Changes and Clinical Course in 118 Cases of Calculous Cholecystitis*

Pathologic Lesion Present	No. Cases	Duration of Symptoms				Period of Preparation	Average Postoperative Period in Hospital	Results of Follow-Up Study				No. Without Follow-Up Study
		1 Yr.	1-5 Yr.	5-10 Yr.	Over 10 Yr.			Died	Well	Improved	Unimproved	
Cholecystectomy (110 Cases, with Follow-Up in 62)												
Acute gangrenous cholecystitis	13	5	8	0	0	2.4 days after admission (12 cases), 41 days (1 case)	13.6 days	0	4	4	0	5
Acute ulcerative cholecystitis	3	3	0	0	0	3.6 days	18.3 days	0	0	2	0	1
Acute exacerbation; chronic cholecystitis	6	2	0	0	4	3.5 days	13.0 days	1	2	1	0	2
Subchronic cholecystitis	41	5	15	14	7	9.2 days	15.4 days	2	14	8	0	17
Chronic cholecystitis	47	8	21	7	11	8.7 days	14.2 days	3	13	13	1	17
Total	110	23	44	21	22			6	33	28	1	42
Cholecystostomy (8 Cases)												
Acute ulcerative cholecystitis	1	0	1	0	0	Immediate (3 cases), 10.5 days (4 cases)	26.4 days	1	0	0	0	0
Acute exacerbation; chronic cholecystitis	6	2	3	1	0			1	4	0	0	1
Chronic cholecystitis	1	0	0	0	1			1	0	0	0	0

2. The cholecystogram is the most important single clinical test in establishing a positive diagnosis of disease of the gallbladder. Rose [13] summarized the work of 20 authors, reporting a total of 39,280 cases, in 5,983 of which operation was performed, and added 911 cases of his own, in 295 of which operation was performed. He concluded that the roentgenographic diagnosis of a pathologic process of the gallbladder is dependable to the extent of 98 per cent. Ferguson and Palmer,[14] in a review of 2,070 cases extending over a period of five years, arrived at approximately the same conclusions as Rose. However, the roentgenographic diagnosis of a normal gallbladder is correct, on the average, in only about 76 per cent of the cases. This finding may be explained, according to Burden,[15] by his observation that an incompetent sphincter of Oddi will not permit of proper filling of the gallbladder or of concentration of its contents. On the other hand, a spastic sphincter, which

TABLE 3.—*Correlation of Pathologic Changes with Clinical Symptoms and End-Results in 118 Cases of Calculous Cholecystitis*

Pathologic Lesion Present	No. of Cases	Jaundice	Qualitative Dyspepsia	Colic	Well	Improved	Unimproved
Acute gangrenous cholecystitis	13	4	3	13	4	4	0
Acute ulcerative cholecystitis	4	1	0	4	0	2	0
Acute exacerbation; chronic cholecystitis	12	4	5	12	2	1	0
Subchronic cholecystitis	41	10	19	39	14	8	0
Chronic cholecystitis	48	12	17	44	13	13	1
Total	118	31	44	112	33	28	1

is frequently present in cases of cholecystitis, will allow and even promote proper filling and concentration in the gallbladder, thus giving rise to a normal cholecystogram even though the gallbladder is diseased.

According to the statistics of Moore,[16] Hauser,[2] Clute and Swinton [17] and Hitzrot,[12b] the diagnosis based on the cholecystogram is correct in 90 per cent of the cases and is of equal value whether the dye is given by mouth or intravenously. Persistence of the shadow after a fatty meal is indicative of a pathologic condition of the gallbladder. In

13. Rose, C. B.: Some Problems and Results in Cholecystography, Radiology **22**:197-201 (Feb.) 1934.

14. Ferguson, A. N., and Palmer, W. L.: Cholecystography: Its Clinical Evaluation; Study of Two Thousand and Seventy Cases, J. A. M. A. **100**:809-812 (March 18) 1933.

15. Burden, V. G.: X-Ray Gall Bladder: Surgical Opinion, Am. J. Surg. **22**:60-63 (Oct.) 1933.

16. Moore, S.: Cholecystography: Analysis After Six and One-Half Years' Application, J. A. M. A. **95**:1957-1961 (Dec. 27) 1930.

17. Clute, H. M., and Swinton, N. W.: Management of Gallstones: Review of Two Years' Experience, S. Clin. North America **14**:1137-1145 (Oct.) 1934.

comparison with a positive clinical history and a positive cholecystogram, the icterus index, the qualitative and quantitative van den Bergh tests, duodenal drainage and fractional analysis of the gastric contents are only of secondary importance in the diagnostic armamentarium.

A glance at table 4 shows that in our group of 133 patients cholecystographic studies were done on 58. The cholecystographic picture was correct, as far as disease of the gallbladder other than stone is concerned, in 82.7 per cent. The diagnosis as to the presence or absence of stone was made correctly by the cholecystogram in only 51.7 per cent of the patients studied. The latter results may be explained by the fact that about 60 per cent of biliary calculi are radiolucent and are therefore not visualized by the cholecystogram. Flat roentgenograms were made of only 8 patients, with a 50 per cent correct diagnosis for the presence or absence of stone.

TABLE 4.—*Correlation of Cholecystogram and Flat Roentgenogram with the Operative and Pathologic Pictures*

	Absence of Stone*		Presence of Stone†	
Roentgenographic Picture	No.	Pathologic Picture	Chronic Cholecystitis	Acute Cholecystitis
Cholecystogram				
Reported normal	2	Chronic cholecystitis	3	1
Nonfilling or poor filling with stone	2	Chronic cholecystitis without stone	19	1
Nonfilling or poor filling without stone	5	Chronic (4 cases), congested (1 case)	18	3
Normal filling with no shadows	1	Chronic	3	0
Flat roentgenogram				
Evidence of stone	1	Subchronic, no stones	2	2
No evidence of stones	0		3	0

* Roentgenographic studies were made on 11 of 15 patients without stone.
† Roentgenographic studies were made on 55 of 118 patients with stone.

3. Laboratory studies are of some diagnostic importance. In spite of the great amount of work that has been done in studying the functions and chemistry of the liver, investigators are still in the dark when they try to evaluate the state of hepatic function in a particular case. The various dye tests and the galactose tolerance test are of some value in estimating some of the functions of the liver but are insufficient to answer the question as to what will be the physiologic response of the liver in a given case in the event that a laparotomy is performed.

Fowler [18] said that in 80 of 100 patients with disease of the gallbladder the symptoms subside or can be successfully treated medically, but he is contradicted by his own statistics, which cover a study of 979 patients. His figures show that a higher mortality and morbidity and failure to obtain relief from symptoms occur in patients who are treated medically for a long time, in whom pathologic processes

18. Fowler, R. S.: Gall Bladder Disease: One Thousand End Results, Am. J. Surg. **22**:53-59 (Oct.) 1933.

pursuant to the disease of the gallbladder are allowed to develop. The greatest factor in deaths from disease of the biliary tract appears to be the delayed operation, which permits of the development of the train of physiologic and pathologic changes that occur with the passing of time.[19] It must be remembered that disease of the gallbladder often affects other surrounding organs [20] besides the liver, frequently causing chronic pylorospasm, pancreatitis and possibly cardiac [21] and renal derangement. Lahey has well said "our medical friends must overcome the complacency with which they permit patients to go through repeated attacks of gall-stone colic" (quoted by Palmer [19a]).

Goldish and Gillespie [22] showed that the average age of the patients who have died after operation for disease of the gallbladder is 10.3 years greater than that of those who lived. Heuer [23] concluded that the difficulties which beset the surgeon during and after the operation are the results of prolonged disease. The deeply jaundiced patient with obstruction of the common duct, lowered vitality, poor resistance to infection, renal damage and a tendency to hemorrhage presents an example of the result of prolonged disease; such a patient will die all too frequently notwithstanding the best surgical measures.

Of the 9 patients who died after operation (table 5), 7 were women, ranging in ages from 45 to 64 years; 5 gave a history of symptoms relative to the gallbladder extending over five years and 2 over ten years. Although none of these deaths definitely fall into any of the three groups of "liver deaths" as described by Heyd,[24] the liver showed pathologic changes, severe in many instances, in all of the cases in which autopsy was performed. Multiple abscesses of the liver were found in 5 of the 8 patients on whom autopsy was performed, and hepatitis of varying severity was found in 7. All of the 9 with a history of prolonged involvement of the gallbladder showed evidence also of involvement of the pericholecystic structures, the liver, pancreas or kidneys or

19. (*a*) Palmer, D. W.: Preoperative Pathology in Its Relation to Post-Operative Gallbladder Deaths, Ohio State M. J. **30**:293-297 (May) 1934. (*b*) Pratt, G. H.: Cholecystectomy and Cholecystostomy in Acute Suppurative and Gangrenous Cholecystitis, Am. J. Surg. **22**:46-52 (Oct.) 1933. (*c*) Bashein.[11]

20. Mason, J. T., and Blackford, J. M.: Conservative Treatment of Cholecystitis, J. A. M. A. **99**:891-893 (Sept. 10) 1932.

21. Schwartz, M., and Herman, A.: Association of Cholecystitis with Cardiac Affections: Study Based on One Hundred and Nine Cases, Ann. Int. Med. **4**:783-794 (Jan.) 1931.

22. Goldish, D. R., and Gillespie, M. G.: Review of Three Hundred and Forty-Seven Gall Bladder Operations, Am. J. Surg. **21**:30-37 (July) 1933.

23. Heuer, G. J.: Factors Leading to Death in Operations upon Gall Bladder and Bile Ducts, Ann. Surg. **99**:881-892 (June) 1934.

24. Heyd, C. G.: Liver Deaths in Surgery of Gallbladder, J. A. M. A. **97**: 1847-1848 (Dec. 19) 1931.

TABLE 5.—*Analysis of Cases of Cholecystitis in Which Death Occurred After Cholecystectomy and Cholecystostomy*

Case No.	Patient	Age	Sex	Duration and Symptoms	Period Covered by Past History	Period Before Operation	Operation	Operative Findings	Clinical Course	Time of Death After Operation	Necropsy
1	A.B.	46	F	5 days; jaundice; colic	6 yr.	7 days	Cholecystostomy	Acute ulcerative calculous cholecystitis; stone in cystic duct; abscess of gallbladder bed	Paralytic ileus	3 days	Acute ulcerative cholecystitis; abscesses of liver; localized peritonitis; fatty infiltration of pancreas
2	M.D.	64	F	1 mo.; colic and dyspepsia	12 yr.	1 day	Cholecystostomy	Shrunken gallbladder; many stones; stone in cystic duct; hepatitis; adhesions	Septicemia; positive blood culture	4 days	Chronic cholecystitis; abscesses of liver; localized peritonitis; periportal cirrhosis
3	R.S.	55	F	3 wk.; jaundice; colic; dyspepsia	12 yr.	10 hr.	Cholecystectomy; choledocholithectomy	Gangrenous cholecystitis; stone in common bile duct; adhesions	Severe postoperative shock; hematemesis	5 days	Subchronic exacerbation of focal necrosis; abscesses of liver; infarction of liver; portal cirrhosis
4	A.G.	40	M	10 days; chills; fever; jaundice	6 yr.	6 days	Cholecystectomy; appendectomy	Chronic calculous cholecystitis; appendical abscess	Chills, fever and intestinal obstruction	47 days	Suppurative pylephlebitis of portal vein; abscesses of liver; gangrene of small intestines
5	E.B.	46	F	2 wk.; qualitative dyspepsia	7 yr.	1 day	Cholecystectomy	Chronic cholecystitis; adhesions	Intestinal obstruction due to adhesions	3 days	Chronic cholecystitis; adhesions producing obstruction; postoperative shock; fatty infiltration of liver and pancreas
6	P.B.	48	F	4 days; vomiting; fever; uremia	5 yr.	7 days	Cholecystectomy	Chronic calculous cholecystitis	Abdominal distention; pulmonary atelectasis	13 days	Multiple hemorrhagic areas; necrosis and hepatitis; purulent bronchitis
7	B.M.	45	F	2 mo.; chills; fever; jaundice; colic	5 yr.	37 days	Cholecystectomy; choledochotomy	Chronic calculous cholecystitis; pericholecystic adhesions; induration of liver and pancreas	Hematemesis; melena; hemorrhage from operative site	20 days	Secondary hemorrhage from operative site; diffuse hepatitis; abscesses of kidneys
8	A.J.	60	F	3 mo.; colic; qualitative dyspepsia	10 yr.	26 days	Cholecystectomy	Acute exacerbation; chronic calculous cholecystitis; pericholecystic adhesions	Circulatory collapse; laparotomy showed no hemorrhage	1 day	No necropsy
9	J.F.	35	M	1 day; fever; colic	0	10 hr.	Cholecystostomy	Acute gangrenous calculous cholecystitis	Abdominal distention; anuria; uremia on third day after operation	7 days	Uremia; gangrenous cholecystitis; local peritonitis; adhesions; portal cirrhosis; fatty infiltration of pancreas; congenital aplasia of right kidney; toxic nephrosis

combinations of these organs. The presence of adhesions in 6 of these patients made operation more difficult. In case 5 the many adhesions present caused intestinal obstruction and finally death. The patient in case 2 died of septicemia, which undoubtedly was present but unrecognized prior to operation. A blood culture taken on the day after the operation was positive for Friedländer's bacillus. Case 4 should not really be listed under "gallbladder death," although the history pointed to disease of the biliary tract. Operation in this case revealed besides chronic calculous cholecystitis, an appendical abscess in which the appendix had sloughed off. Suppurative pylephlebitis with multiple abscesses of the liver and infarction and gangrene of several feet of small intestine developed, and the patient died. In case 9 anuria developed within twenty-four hours postoperatively, and the patient died six days later of uremia. This case might be regarded as an example of the "hepatorenal" syndrome described by Schutz and his co-workers.[25]

COMMENT AND SUMMARY

We have presented a clinical and pathologic review of disease of the gallbladder in 133 patients who were operated on at the Mount Sinai Hospital from 1930 to 1935. Of this group, we have been able to obtain informative follow-up data on 83 persons. Although our group is too small to permit drawing definite conclusions regarding any single phase of disease of the gallbladder and its treatment, nevertheless, we feel that we are justified in stressing the following observations:

1. The clinical history of biliary colic, and to a lesser extent of qualitative dyspepsia for fried and fatty foods and of jaundice, is of primary importance in the establishment of a diagnosis of disease of the biliary tract. Of the clinical tests, the cholecystographic study is the most important, and in our series of 58 cases a correct diagnosis was made in 82.7 per cent.

2. The results of cholecystectomy on patients with noncalculous cholecystitis were better when the patient presented a definite history of biliary colic and a definite pathologic process was found at operation. Cholecystectomy on patients with noncalculous cholecystitis in whom the pathologic process was minimal and the clinical history of biliary colic was not definite resulted in relief of symptoms in only about 56 per cent as compared to cure or great improvement in 67 per cent of those giving a definite history of biliary colic.

3. Our follow-up data on 63 patients with calculous cholecystitis showed that the clinical results are far better in those with stone than

25. Schutz, C. B.; Helwig, F. C., and Kuhn, H. P.: Contribution to Study of So-Called Liver Deaths, J. A. M. A. **99**:633-636 (Aug. 20) 1932.

in those without stone. Of the 63 patients about whom information was obtained, 62 were either cured or greatly improved, a percentage of 98.4 as compared to the 63.2 per cent of the noncalculous group.

4. The results following cholecystectomy on 22 patients with acute cholecystitis included in our group with calculous cholecystitis indicate that a radical operation as soon as the patient has been adequately prepared is the desirable mode of treatment. Of the 22 patients presenting acute gangrenous, acute ulcerative or an acute exacerbation of chronic cholecystitis, only 1 died after operation. Both the morbidity and the mortality in the cases of acute cholecystitis were less after cholecystectomy than after cholecystostomy.

5. Our review of disease of the biliary tract in 133 patients has shown that there is a direct relationship between the duration and the severity of the clinical symptoms, the morbidity and mortality and the character of the pathologic lesions noted at operation and at necropsy. The significant part which the pericholecystic complications, the result of prolonged medical treatment for disease of the gallbladder, played in the fatal outcome of the 9 patients justifies a plea for early operative treatment of patients suffering with disease of the biliary tract after a definite diagnosis has once been established.

Drs. B. Lipshutz, M. Behrend and E. L. Eliason granted permission for the inclusion of their cases in this report.

CARCINOMA OF THE SUPRAPAPILLARY PORTION OF THE DUODENUM

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The purpose of this communication is to report six cases of carcinoma of the suprapapillary segment of the duodenum and to analyze and summarize the data obtained from the reported cases of this condition. Reports of one hundred and four cases were abstracted from the literature, thirty-five [1] of which were regarded as acceptable on the basis of the data presented, a clinical history and gross and microscopic studies of the primary lesion being presented in each report. Twelve [2] additional cases, although probably authentic examples of this condition, could not be included in the present analysis because of insufficient clinical or pathologic data. Fifty-seven more reported cases were discarded, nineteen because, owing to involvement of the stomach, pancreas or bile passages in the malignant process,[3] the duodenal origin of the lesion was not established with certainty and thirty-eight [4] because the histologic

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From the Pathological Laboratories of the Jefferson Medical College and Hospital, the Jefferson Hospital Tumor Clinic and the Philadelphia General Hospital.

1. Coupland; Ewald; Montgomery and Sherman; Pic (case 1); Letulle; Aaron; Gerster; Geiser (case 1); Bibby and Stewart; Jefferson; McGuire and Cornish (case 3); Herman and von Glahn; Ramond, Vincent and Clémont (case 1); Van Tienhoven (case 2); Morrison and Feldman; Dewis and Morse (cases 1, 2, 3, 4 and 5); Kettle; Archibald; Pacetto; Lageder; Meyer and Rosenberg (case 2); Mateer and Hartman (case 1); Rutishauser (cases 1 and 5); Cave (cases 8 and 11); Eger (case 1); Lisa; Levine and Fitzhugh (case 2); Dardinski; Ochsner and Wilbur (case 2); von Hrabovsky (case 2); Doub and Jones (case 1—the same as reported by Mateer and Hartman, case 1); McNamara, and Bastos.

2. Geiser (case 4); Peck; Reichel and Staemmler (cases 2 and 3); Borrmann (cases 1 and 2); Arisz (cases 1 and 2); Raiford (cases 46597 and G 662); Bookman; Schüssler (case 1) and Rutishauser (case 4).

3. Fullet; Drechsler; Béringier; Coupland; Höft; Trémolières; Geiser (case 9); Benedict; Bassler and Grant; Lichty (cases 1 and 3); Judd (case 2); Orator (cases 1 and 2); Cabot (case 15111); Hinton (cases 1 and 3); Popovici, and Wilson and Noble.

4. Haley; Carrer; Dickinson; Cayla; Boyé; Whittier (case 12); Pye-Smith; Weecke; Perry and Shaw; Pic (case 2); Günther; Czygan; Heynen; Wurm

(Footnote continued on next page)

studies were not reported, the diagnosis apparently having been made on the basis of gross examination alone. Of historical interest are the cases reported by Hamberger (1746) and Morgagni (1761).

REPORT OF CASES

CASE 1.—J. P., a white man aged 35, whose complaints were belching, vomiting, anorexia and a loss of 30 pounds (13.6 Kg.) in weight, was admitted to the Jefferson Hospital on March 22, 1931, with the clinical diagnosis of carcinoma of the head of the pancreas. For years he had been troubled with gas and belching. In November 1929 he experienced a brief attack of severe epigastric pain, which was followed a week later by jaundice. At operation on Jan. 2, 1930, in another hospital, a markedly thickened gallbladder containing many stones was removed, together with several drachms of gravel from the common bile duct, which was incised and drained. Jaundice did not entirely disappear owing to obstruction at the ampulla of Vater, and the drainage tube could not be removed from the common duct. A choledochogastrostomy stoma was then established, and the jaundice cleared entirely, the patient remaining practically free from symptoms until February 1931. Again jaundice recurred, associated with vomiting, excessive gas and pain in the right upper abdominal quadrant, and the patient was admitted to the Jefferson Hospital on March 22.

Physical examination revealed tenderness in the right upper abdominal quadrant and a palpable mass, which descended with inspiration. The hemoglobin content of the blood was 27 per cent, the red cell count 1,280,000, the white cell count 1,100 and the color index 1.01. There were polychromasia and stippling, with many microcytes, macrocytes and poikilocytes. The urine was alkaline, contained albumin and had a high specific gravity varying from 1.016 to 1.030. The stools contained blood and an excessive amount of fat. There were blood and bile in the vomitus, which showed a free acidity of 18 and a total acidity of 28. A roentgenogram of the gastro-intestinal tract was unsatisfactory because of considerable retention of food. With treatment the hemoglobin content increased to 43 per cent, the red cells to 2,850,000 and the white cells to 8,200. At laparotomy on April 14, local anesthesia being used, the stomach appeared pale and distended and the jejunum pale and collapsed. On account of dense adhesions it was not possible to make a satisfactory examination of the duodenum and bile ducts. A large, irregular, firm, slightly tender mass, 7.7 cm. in diameter, was palpated in the retroperitoneal region, and a posterior gastro-enterostomy was performed in the usual manner. That night there was slight oozing of blood from the wound, the patient was markedly dehydrated, the chloride content of the blood was 406.9 and the carbon dioxide-combining power rose from 98 to 128. Fluids were administered subcutaneously and intravenously, and a small transfusion of blood was given. The following evening the pulse became rapid and the temperature high, and there was a marked drop in the blood pressure. The patient died from hemorrhage on March 17.

Autopsy was performed four hours after death. The combined gross anatomic and microscopic diagnoses were: (1) annular constricting adenocarcinoma of the

(cases 1 and 2); Friedrich (cases 1 and 2); Moynihan (cases 1 and 2); George and Leonard; Helm; Judd (cases 1, 3, 4 and 5); McGuire and Cornish (case 4); Vervloet; Eusterman; Berkman and Swan (cases 1, 2, 3, 4, 5 and 6); Brüning; Dewis and Morse (cases 8 and B); Hanganutz, and Brdiczka.

suprapapillary portion of the duodenum with constriction of the common bile duct and extension and metastases to the pancreas, regional lymph nodes and surrounding tissues; (2) hydrohepatosis with marked jaundice; (3) chronic interstitial pancreatitis; (4) recent gastro-enterostomy; (5) peritoneal, pericardial and bilateral pleural effusions, and (6) pulmonary edema and congestion.

Dense fibrous adhesions passed between the fossa of the gallbladder and the lower end of the stomach and duodenum, including the inferior margin of the liver, which was adherent to the anterior abdominal wall. The lumen of the duodenum just proximal to the ampulla was practically completely obliterated by an annular constricting lesion. The mucous membrane in this area appeared thickened and nodular but apparently was not ulcerated. There was marked neoplastic induration of the wall of the duodenum, with direct extension into the pancreas and the surrounding tissue.

The proximal portion of the duodenum and stomach were greatly distended, and the pyloric ring was completely effaced. The lower border of the stomach extended below the umbilicus; its mucosa was atrophic, and its lumen contained bile-stained, bloody fluid. The margins of the gastro-enterostomy opening were intact but swollen and edematous. A choledochogastrostomy opening did not exist, and there was no gallbladder. The lower end of the common bile duct was buried in a mass of adhesions and cancer tissue. A probe was passed with difficulty through the ampulla of Vater into the common bile duct, which was markedly thickened and dilated. The liver was irregular on the surface, and the capsule was thickened and covered with dense adhesions, especially on the under-surface. On section the hepatic tissue was dark greenish brown, the normal markings were absent, there was a good deal of fine fibrosis and the intrahepatic ducts were markedly thickened. Many of the mesenteric, peripancreatic, retroperitoneal and periaortic lymph nodes were enlarged, firm and gray, measuring from 2 to 3 cm. in diameter.

Sections from the constricting lesion in the duodenum showed the mucous membrane to be markedly thickened (fig. 1) and interspersed with large areas of atypical epithelium. Brunner's glands formed a thick, practically continuous submucosal layer. Malignant transformation appeared to occur first in the deeper parts of the mucosa, where the cells became irregular in shape, often rounded, and were closely packed instead of forming crypts. For a space they seemed to respect the muscularis mucosa, penetrating it only in limited small areas. These cells permeated through Brunner's glands (fig. 2), tending to follow the supporting stroma, and on reaching the submucosal areolar tissue spread out laterally almost the entire length of the sections. They infiltrated in and between the muscle bundles, usually at right angles to the length of the section, and were seen deep to the muscle (fig. 3). One large nerve was invaded, and epithelial cells were seen in small veins, arteries and lymphatics. In places the cells formed small acini of cuboidal or columnar cells, but elsewhere there was no characteristic arrangement, the cells being in dense clumps or in slender strands separated by fibrous tissue. The individual cells were variable in size and shape but usually small, with round and ovoid hyperchromatic nuclei, which were sometimes marginal and crescent shaped, giving the cell a signet ring appearance. No mitotic figures were seen. The fibrous stroma was scant in the mucosa but more abundant deep in the wall of the duodenum.

There were marked atrophy and fibrosis of the pancreas within and about the lobules. Lymphocytes were scattered throughout and tended to clump about the ducts, nerves and infiltrating strands of atypical epithelial cells. The tumor

Fig. 1 (case 1).—Section from the constricting lesion in the duodenum, showing marked neoplastic thickening of the mucous membrane; circa × 7.

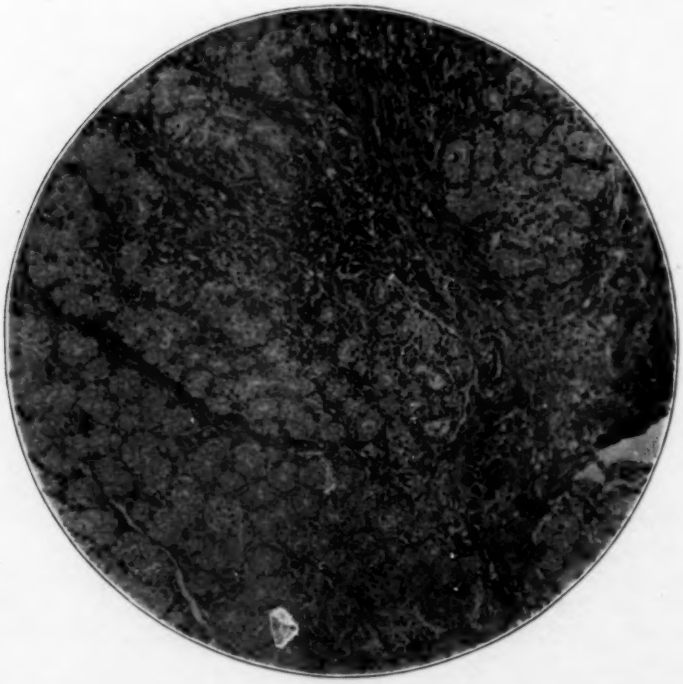

Fig. 2 (case 1).—Section of the duodenal lesion showing neoplastic permeation of Brunner's glands: × 100.

tissue here had a more abundant stroma than in the intestine and was frequently observed surrounding nerves and vessels.

Sections of a lymph node showed almost complete replacement by a dense mass of undifferentiated epithelial cells with little stroma, the atypical appearance of the cells being a striking feature.

The liver presented the characteristic picture of biliary stasis, with granules and droplets of bile pigment, bile casts and degeneration and necrosis in the inner third of the lobule. The sinusoids were dilated, the small bile ducts were proliferated and there was a marked increase in periportal connective tissue, which frequently completely encapsulated the lobules. Scattered throughout the sections

Fig. 3 (case 1).—Section of the duodenum showing a small strip of mucous membrane, Brunner's glands and the underlying muscle. The neoplastic cells have permeated the connective tissue stroma of Brunner's glands and have infiltrated in and between the muscle bundles frequently at right angles to the length of the section; × 50.

were numerous focal midzonal and biliary necroses, which were often converted into small abscesses.

Case 2.—C. N., a white man aged 69, whose complaints were vomiting, constipation, abdominal distress and marked thirst of two weeks' duration, was admitted to the hospital on Jan. 30, 1924, with the clinical diagnosis of carcinoma of the pancreas. During the preceding half year he lost 15 pounds (6.8 Kg.) in weight. The onset of the terminal illness occurred suddenly one evening on Jan. 13, 1923, with the vomiting of a large quantity of light frothy material, unassociated with pain or nausea. The patient returned to work the following

day but vomited that night after the evening meal and on each succeeding night for a week. At first the vomiting was not forceful, but later he had to support his abdomen because of retching. There were tarry stools, slight constipation, a good deal of belching with the attacks of vomiting and frequent eructations of sour fluid. On physical examination the epigastric region was distended and slightly rigid but not tender, and no definite mass was visible or palpable. There were a marked grade of secondary anemia and a leukocytosis of 22,600. The urine had a specific gravity of from 1.017 to 1.025 and contained albumin and casts. The stools contained blood. The gastric content showed a residual total acidity of 34 and free hydrochloric acid of 19; after a test meal these figures gradually rose to a maximum of 49 and 30, respectively, at the end of two hours. Four days after admission the patient fainted after vomiting 100 cc. of thick dark brown material. He regained consciousness after a short interval but was weak, cold and restless and complained of severe pain in the lower part of the abdomen. That night he vomited 250 cc. of bright red blood and died five minutes later.

Autopsy was performed thirteen hours after death. The combined gross anatomic and microscopic diagnoses were: (1) adenocarcinoma of the supra-papillary segment of the duodenum, with extension to the pancreas and metastasis to the liver and peritoneum; (2) duodenal hemorrhage; (3) hemoperitoneum; (4) pulmonary emphysema, congestion and edema; (5) arteriosclerosis of the aorta and renal arteries; (6) chronic nephritis, and (7) fibrosis and degeneration of the myocardium.

In the duodenum just distal to the pylorus was a soft dark reddish green ulcer, 3 by 5 cm., which completely encircled the intestine. The wall of the duodenum was composed of firm gray tissue, which extended laterally in the muscular coat beneath the pyloric ring into the wall of the stomach for 2 cm. The duodenum at the site of the ulcer was bound to the head of the pancreas, which was infiltrated by a tumor mass, 1.5 cm. in diameter, continuous with the lesion in the duodenum. The distal aspect of the duodenal lesion was sharply limited by normal mucosa. The stomach and esophagus were distended with blood. The peritoneum contained several firm gray nodules, measuring from 1 to 3 mm. in diameter, on the under-surface of the diaphragm and in the visceral serosa of the small and large intestine.

The liver weighed 2,080 Gm. and was reddish brown and soft. There were many circumscribed firm gray nodules, averaging 2 cm. in diameter, which formed a large confluent mass in the edge of the right lobe. The largest of these nodules showed necrotic centers, while those on the surface were regularly umbilicated. The biliary passages were patent.

There were bilateral congestion and edema of the lungs and several small, firm, discrete, pearly gray subpleural nodules.

Histologic sections of the duodenal lesion disclosed a transition from normal mucous membrane into a large area of atypical epithelial cells showing extensive necrosis and hemorrhage. Lateral to the area of ulceration Brunner's glands were hyperplastic, but immediately underneath it they were destroyed by the cancer tissue, which permeated the stroma of these structures. The tumor cells penetrated through all coats of the intestine and spread out laterally into the surrounding fat along the peritoneal surface. The cells were discretely arranged, large, round or oval elements with acidophilic or basophilic vacuolated cytoplasm and relatively small oval or sickle-shaped hyperchromatic nuclei, which were often eccentrically situated. Other nuclei were large and pale with multiple lobulations and occupied

a more central position in the cell. Mitotic figures were rare. A large amount of stringy mucinous material was present between the cells and in the cytoplasmic vacuoles. The tumor cells were further separated into nests and linear masses by strands of avascular connective tissue infiltrated with small round cells. In the depths of the main tumor a few acini lined with cuboidal and columnar cells were observed, and many large blood vessels contained tumor cells.

The large tumor nodules in the liver showed extensive hemorrhage and necrosis. The atypical epithelial cells grew in solid nests in some places, but mainly they were desquamated into small alveolar spaces enmeshed in stringy mucinous material. As a rule the cells had an abundance of finely vacuolated cytoplasm, which contained droplets of mucin. Many nuclei were oval and eccentrically placed in the cell, while others were large, irregular and hyperchromatic. The stroma was abundant and hyalinized.

In the under-surface of the diaphragm the tumor cells formed nests and acini supported by dense connective tissue stroma, and there was little tendency to extend below the serosal surface.

CASE 3.—M. C., a physician aged 58, a morphine addict, was admitted to the hospital in a moribund condition on April 15, 1916. A few days previously he had been picked up unconscious from the floor of his home and put to bed by an attendant, who reported that the patient had subsequently passed large quantities of blood by bowel. Because of his stupor and delirium it was difficult to make a satisfactory physical examination during the period of hospitalization, and the findings contained in the clinical record were of little significance with regard to the lesions disclosed at autopsy. It was observed that the patient passed blood by bowel several times. The urine was acid, contained hyaline casts and had a specific gravity of 1.016. The hemoglobin content was 29 per cent, the red cell count 1,880,000, the white cell count 11,600 and the color index 0.8. The patient died two days after admission without regaining consciousness.

Autopsy was performed thirteen hours after death. The combined gross anatomic and microscopic diagnoses were: (1) papillary scirrhous adenocarcinoma of the first portion of the duodenum, with metastasis to the liver and peritoneum; (2) hemorrhage into the intestinal tract; (3) calculous cholecystitis; (4) sclerosis of the aortic and mitral valves; (5) arteriosclerosis of the aorta; (6) acute degeneration of the myocardium and kidneys; (7) cerebral and pulmonary edema, and (8) a small hemorrhagic peritoneal effusion.

An annular ulcer, 5 cm. in diameter, was found in the first portion of the duodenum immediately adjacent to the pyloric sphincter. The edges were hard, indurated and sharply outlined, while the floor was irregular and nodular and contained a small thrombosed vessel. The wall of the duodenum opposite the ulcer was adherent to the neck of the gallbladder. The stomach was markedly dilated, while the remainder of the bowel was dilated and filled with black material.

The peritoneal cavity contained a small amount of blood-tinged fluid. The serosa was smooth, moist and glistening, except for a few small irregular neoplastic nodules on the under-surface of the diaphragm and the right pelvic wall.

The liver was large, soft and pale and contained many firm gray nodules, measuring from 1 to 4 cm. in diameter. The gallbladder was adherent to the wall of the duodenum and the lumen contained 25 cc. of viscid yellow bile and three small faceted calculi.

Microscopic sections of the duodenum disclosed a transition from normal mucosa to an ulcerated neoplastic lesion infiltrating laterally along the submucosa and extending deeply through the muscular wall to invade the peritoneum and

superficial fatty tissue. The tumor cells were usually cuboidal or columnar, but many showed marked variation in size and staining with from one to several hyperchromatic nuclei. A few were observed in mitosis. The cells grew in small nests of imperfect strands but tended generally to reduplicate simple or papillary acinous structures and showed necrosis in many areas. The stroma was abundant, consisting of compact strands of collagenous fibers with a few young and old fibroblasts but not many blood vessels. There was a marked inflammatory reaction consisting of lymphocytes, chiefly limited to the muscular coats along the line of penetration of the tumor cells.

In the liver the atypical epithelial cells appeared to grow along the sinusoids and within the spaces remaining after absorption of necrotic hepatic cells.

CASE 4.—A. W., a white woman aged 85, was admitted to the Philadelphia General Hospital on March 29, 1929, with the clinical diagnosis of chronic intestinal obstruction. According to the clinical record, she had a stroke of apoplexy five years previously followed by impairment of the mental faculties. The terminal illness apparently began in January 1929, with black feces, vomiting and anal pain, both the vomitus and the feces being black. About the middle of March she became bedfast and refused all food; the vomiting continued, and there were no bowel movements until she entered the hospital two weeks later. On physical examination no noteworthy findings were recorded except that the tissues were dehydrated and râles were heard over the thorax. Death occurred suddenly on March 30.

Autopsy was performed twelve hours after death. The combined gross anatomic and microscopic diagnoses were: (1) obstructing primary scirrhous adenocarcinoma of the suprapapillary portion of the duodenum with extension and metastases to the pancreas, the liver and the wall of the gallbladder; (2) calculous cholecystitis; (3) chronic pancreatitis with fatty infiltration; (4) arteriosclerosis of the aorta and the coronary and renal arteries with chronic nephritis, and (5) pulmonary congestion.

The lumen of the duodenum 5 cm. distal to the pylorus was narrowed by a round elevated, indurated ulcer, 2 cm. in diameter. The entire intestinal wall immediately subjacent was firm, indurated, grayish white and adherent both to the pancreas and to the gallbladder. There were no appearances suggesting pancreatic invasion. The gallbladder was contracted about several small faceted greenish yellow concretions together with a small amount of dark grumous bile. On the peritoneal surface near the fundus were two or three small round, grayish white nodules. Its wall was considerably thickened, especially in the region of the neck, which was involved by masses of tumor tissue in the duodenum and liver. The liver weighed 1,120 Gm.; it was firm, and its capsule was thickened; a few grayish white nodules with central yellowish necrotic areas were scattered through the parenchyma. The quadrate lobe was practically entirely replaced by tumor tissue and was densely adherent to the immediately contiguous upper portion of the gallbladder. It was not possible to determine at autopsy whether the tumor arose primarily in the gallbladder, liver or duodenum, but the probabilities were stated in that order, the duodenum being considered the least likely primary site.

The stomach was markedly dilated, and its outline resembled the curve of a fish-hook with the lower border almost at the symphysis pubis. The walls of the stomach were hypertrophied, and the rugae were absent. The body tissues were not jaundiced, and there was no evident obstruction of the biliary passages.

Microscopic sections of the duodenum showed a pale-staining, partially autolyzed mucous membrane, which merged abruptly with an ulcerated area covered with

atypical epithelial cells. The area of ulceration remained comparatively superficial and did not extend below the deep portion of the submucosa. All the coats of the duodenum, however, were involved by cancer tissue. Brunner's glands were completely absent from the area of ulceration but showed no abnormalities in the adjacent portion. The atypical epithelial cells penetrated through all coats of the duodenum and were distributed singly, in small clumps and nests, only rarely reduplicating acinous structures. The cells showed an extreme degree of irregularity in size, shape, staining and number of nuclei; most of them were polyhedral and spindle shaped, with relatively large nuclei and scanty acidophilic cytoplasm, which was usually granular and occasionally contained vacuoles. The cells lining the acinous structures were often cuboidal or columnar. Most of the nuclei were oval or indented and generally enlarged; many were distorted and hyperchromatic, while the largest ones were frequently lobulated, and a few contained inclusions. Only a few mitotic figures were observed. In the musculature tumor cells were observed in small spaces in nerves, and the walls of blood vessels and occasionally in their lumens.

The pancreas showed interstitial fibrosis, fatty infiltration and considerable autolysis. A small area of infiltrating neoplastic cells was noted in one of the large connective tissue septums.

In the liver, in contrast to the duodenum, the tumor cells were more regular, more frequently in mitosis, tended generally to reduplicate acinous structures and showed less supporting stroma. Several of the larger areas of tumor tissue contained central areas of necrosis.

The mucosa of the gallbladder was autolyzed, although the structural outlines of its stroma were well preserved and showed no involvement by tumor tissue. The wall in general and the peritoneal coat especially were markedly thickened, fibrotic and infiltrated with small round cells. The outer portion of the wall was invaded by small clumps of atypical epithelial cells, which stopped short of penetrating through to the mucous membrane.

Nothing was observed microscopically to suggest a cholecystic origin of the tumor. The contracted, thickened and fibrotic character of the gallbladder, together with the presence of biliary calculi and the contiguous relationship the gallbladder bore to the neoplastic lesions in the liver and duodenum, could readily suggest such an origin. A careful evaluation of the anatomic and histologic data warrants the conclusion, we believe, that the lesion under consideration was duodenal in origin. The tumor masses in the gallbladder can be accounted for by extension and metastasis, probably by way of local adhesions, the result of preexisting calculous cholecystitis.

Case 5.—I. T., an emaciated white woman aged 66, was admitted to the Philadelphia General Hospital on Oct. 21, 1923, with vomiting, loss of weight and weakness. There was a history of an operation for gallstones eight years previously and shortly after that one for "abscess of the stomach." Late in 1922 the patient began to complain of nausea, loss of weight and strength and a feeling of heaviness in the abdomen. In August of the next year frank epigastric pain developed, and the patient vomited constantly. There was no relationship between the taking of food and the onset of epigastric pain, and no blood was detected in the vomitus. On physical examination several nodules believed to lie in the deep fascia were felt in the abdominal wall, which was thin and doughy in consistency. The other resistant masses were palpated in the region of the stomach, the largest of these being 5 cm. in diameter. The patient's course in the hospital was characterized by restlessness, persistent vomiting and progressive weakness and stupor; death occurred on October 24.

Autopsy was performed twelve hours after death. The combined gross anatomic and microscopic diagnoses were: (1) papillary adenocarcinoma of the first portion of the duodenum with metastases to the liver and lungs and the mesenteric and peribronchial lymph nodes; (2) chronic interstitial pancreatitis; (3) arteriosclerosis of the renal arteries with chronic nephritis; (4) chronic adhesive pleuritis and pericarditis; (5) pulmonary edema, and (6) chronic interstitial myocarditis.

Fig. 4 (case 5).—Section of the duodenum showing hyperplastic changes in the muocus membrane and neoplastic involvement of all coats of the intestine; circa $\times 7$.

The duodenum contained a small firm ulcer which measured 2 cm. in diameter and was located 5 cm. from the pylorus and 1 cm. proximal to the papilla of Vater. The margins of this lesion were elevated, indurated and thrown into folds over the central crater-like ulcer. Proximally the stomach and duodenum were dilated, and the wall of the latter was hypertrophied. The regional lymph nodes were enlarged and, with the head of the pancreas, were densely adherent to the wall of the duodenum opposite the primary lesion.

The liver was enlarged in its left lobe and contained many firm white, opaque nodules, measuring from 1 to 5 cm. in diameter. The gallbladder was absent, and the bile ducts were patulous.

Microscopic sections of the duodenum showed a transition from normal mucosa into a zone of hyperplastic and ultimately atypical epithelial cells with a papillary acinous arrangement (figs. 4 and 5). These cells penetrated all coats of the duodenum, including the serosa, which was thick and fibrotic. Brunner's glands were not very numerous and in several places were partially destroyed by invading tumor cells. The malignant transformation appeared to occur first in the superficial cells of the surface mucosa and gradually extended to

Fig. 5 (case 5).—Section of the duodenum showing a transition from normal mucosa into a zone of hyperplastic atypical epithelial cells with a papillary acinous arrangement. The tumor cells penetrate deeply into the submucosa and muscular coat; × 40.

involve the entire thickness of the mucous membrane, the crypts of the glands being involved last. The connective tissue stroma of the mucous membrane near the point of transition was thickened by infiltrating lymphocytes and plasma cells. Some glands were abnormally short, and others were dilated, long and tortuous. The acinous structures were coarse and irregular, with numerous large branches and ramifying cavities lined by from one to several layers of atypical epithelial cells. The lumens of these cystic structures varied in caliber; some contained papillary spurs which grew out perpendicular to the wall, while others were filled with viable or necrotic tumor cells or acidophilic detritus. The majority of the cells were tall columnar elements with rectangular nuclei, while others were

cuboidal or flattened, and a few were greatly enlarged and polyhedral. The nuclei were pale and vesicular and usually situated near the base of the cell. A few were large, irregular and lobulated. Mitotic figures were present but not numerous. The cytoplasm of the atypical cells was abundant, deeply acidophilic and frequently contained single large vacuoles but little if any mucin. Extensive areas of necrosis were present throughout the tumor tissue. The stroma was loose, comparatively scanty and not very vascular. It was infiltrated with clumps of small round cells and leukocytes on the surface of the lesion and around the necrotic areas.

In the liver the tumor nodules were more solid and cellular, with less stroma and inconspicuous acinous and papillary formation.

CASE 6.—E. H., a white man aged 44, entered the Philadelphia General Hospital on April 5, 1913, with gastric pain and jaundice. Pain began eight months previously, coming on after meals in association with belching, but later it assumed a hot burning character and became continuous. The patient was generally constipated and occasionally noticed gross evidence of blood in the stools. Jaundice developed several weeks before admission, but vomiting was never a symptom.

On physical examination jaundice was marked and emaciation extreme. There was fulness of the right upper quadrant, but the remainder of the abdomen was flat. The liver was felt 4.5 cm. below the costal margin, and the left lobe contained a few palpable nodules. Beneath the liver was a tense pear-shaped tumor mass, which moved with respiration.

The patient's course in the hospital was progressively downward. He began vomiting every day at first and finally almost hourly. The vomitus contained large quantities of fresh and of digested blood. An interesting observation was made at the end of the first week, when it was noted that the yellow color of the skin had lightened perceptibly and the gallbladder was barely palpable. The following day, however, the gallbladder became as large as it was formerly.

The urine was acid, had a specific gravity of 1.018 and contained bile. The red cell count was 2,600,000, the hemoglobin content 35 per cent and the leukocyte count 17,000. Blood was present in the feces. The vomitus was green and contained blood and hydrochloric acid. Death occurred on April 21.

Autopsy was performed forty-six hours after death. The combined gross anatomic and microscopic diagnoses were: (1) adenocarcinoma of the suprapapillary portion of the duodenum with extension to the pancreas and metastasis to the liver; (2) hydrohepatosis with marked jaundice; (3) chronic interstitial pancreatitis with extreme atrophy; (4) dilatation of the stomach; (5) hemorrhage into the stomach and intestines; (6) slight myocardial fibrosis; (7) congestion and edema of the lungs; (8) pulmonary anthracosis and emphysema, and (9) arteriosclerosis of the kidney with chronic nephritis and parenchymatous degeneration.

The first part of the duodenum was the seat of an extensive area of ulceration with ragged edges, about 5 cm. in diameter. Directly beneath this lesion was a firm white mass the size of a fist, involving the wall of the duodenum and the head of the pancreas. The remainder of the pancreas was small, white and firm, and the usual lobular appearance was indistinct. The stomach was greatly dilated and contained coffee-ground material. The intestines were distended with gas and bright red blood.

The liver measured 27 by 19 by 8 cm. and extended 3 fingerbreadths below the ribs. It was dark, olive green, tough and resistant to incision. A number of firm white nodules, measuring up to 3 cm. in diameter, were scattered through

the parenchyma. On the surface the centers of these lesions were slightly depressed. The gallbladder was distended with thick bile, little of which could be expressed through the ampulla of Vater.

Microscopic sections of the duodenum showed all the coats infiltrated with masses of irregular tubules composed of a columnar type of cell lying in a framework of adult connective tissue. The stroma was abundant and infiltrated with round cells and polymorphonuclear leukocytes, especially in areas in which the tumor cells were necrotic. A few mitotic figures were observed.

ETIOLOGY

There is a considerable literature devoted to a discussion of the origin of carcinoma of the suprapapillary segment of the duodenum from duodenal polyps, accessory pancreatic tissue, misplaced remnants of gastric mucous membrane, simple ulcer, Brunner's glands and the minor papilla of Santorini. However, definite proof of any such etiologic relationship is lacking. Ochsner and Wilbur stated that in their case the minor papilla of Santorini was apparently the site of origin for the neoplasm. Although such an origin is possible, this view has yet to be substantiated.

The origin of the tumor from Brunner's gland was postulated in three cases (Ramond; Vincent and Clément; Pic, and Rutishauser's case 1). In the first two no evidence was presented to substantiate this point of view. Rutishauser, however, wrote at length regarding the fine histologic changes in Brunner's glands, which led him to believe that the tumor in his case originated in these structures. In view of the fact that the postmortem examination on Rutishauser's subject was held two days after death, these histologic details would appear to be of little value. These glands were described as hyperplastic in several other cases, but as they normally vary quantitatively in different areas of the suprapapillary segment of the duodenum, the significance of this observation is debatable. Morrison and Feldman noted that these glands were numerous in the vicinity of the carcinoma in their case but were correct in interpreting this feature on the basis that the tumor originated well up in the duodenum where the glands are normally numerous. In our cases Brunner's glands were frequently destroyed by marked inflammation, ulceration and neoplastic permeation of their stroma.

Most simple ulcers are located in the first 2.5 cm. of the duodenum, and it follows that if this condition is a precancerous lesion, carcinoma should occur rather commonly in this situation, and a proportionately large number should be confined to or at least border on this area. An analysis of this series does not support this hypothesis, for in the relatively few cases in which the lesion was situated above the papilla no significant difference could be established in its occurrence in any particular portion of the suprapapillary segment. After evaluating the

evidence dealing with the association of simple ulcer and carcinoma, we are of the opinion that no proof exists to support the hypothesis that simple ulcer of the duodenum is a precancerous lesion.

AGE AND SEX; INCIDENCE

In the series of cases studied twenty-six of the patients were men (three Negroes), varying in age from 35 to 78, with an average age of about 57, and fifteen were women, varying in age from 23 to 85, with an average age of about 55.

Three of our six cases were discovered at the Jefferson Hospital in 3,526 autopsies and the others at the Philadelphia General Hospital, two between Jan. 1, 1920, and Dec. 31, 1935, 20,176 autopsies having been performed during that period.

ANATOMY

The suprapapillary portion of the duodenum extends from the pyloric sphincter to the papilla of Vater and includes, according to academic anatomy, the superior portion and the proximal part of the descending portion. The superior portion, commencing at the pylorus and measuring approximately 5 cm. in length, passes backward, upward and to the right, ending at the neck of the gallbladder. It is in relation above and in front with the quadrate lobe of the liver and the gallbladder, behind with the gastroduodenal artery, the common bile duct and the portal vein and below and behind with the head and the neck of the pancreas. The proximal descending portion, measuring from 3 to 5 cm. in length, extends from the neck of the gallbladder along the right side of the vertebral column to the papilla of Vater. It is in relation in front with the duodenal impression on the right lobe of the liver and the transverse colon; behind it has a variable relationship to the front of the right kidney in the neighborhood of the hilus; the renal vessels, the inferior vena cava and the psoas muscles below are also behind it; at its medial side are the head of the pancreas and the common bile duct; to its lateral side is the right colic flexure. The common bile duct and pancreatic duct together perforate the medial side of this portion of the intestine obliquely from 7 to 10 cm. from the pylorus. The accessory pancreatic duct sometimes pierces it about 2 cm. above and slightly in front of these.

The antrum, or bulbus duodenale, is a part of the superior portion of the duodenum and is directly continuous with the pylorus. In contrast to the remainder of the duodenum, its beginning portion is more freely movable and its relationship to the pancreas much looser. Schwarz has emphasized the close association of the superior portion to the stomach, both having a similar type of mesenteric fixation, similarity in behavior and appearance of the mucous membrane and similar secretory elements.

He regarded this portion of the duodenum as the "after stomach," with a smooth inner surface as differentiated from the remainder of the duodenum, which contains Kerkring folds. Åkerlund made roentgenographic studies of the stomach and duodenum in corpses, these organs being fixed in situ with formaldehyde and filled with contrast masses. Comparisons of these roentgenograms with the anatomic preparations showed that in the majority the shadow of the bulbus corresponded to the entire superior portion. Åkerlund also stated that the filling, emptying, peristalsis and tonus of the duodenal bulb are in large measure independent of the remainder of the duodenum and expressed the belief that it is an anatomic roentgenographic and physiologic entity. That portion of the duodenum from the neck of the gallbladder to the papilla of Vater is occasionally designated as postbulbar (Rutishauser).

MORBID ANATOMY

The tumor measured from 0.4 to 4 cm. in length in twenty-three cases and from 4.5 to 8 cm. in thirteen cases, and in one instance the growth involved 13 cm. of the duodenum. There was a localized growth in twenty-eight instances, thirteen of which were in the bulbar portion, eight at the superior angle and seven near the papilla of Vater. The majority of nonannular localized lesions were situated on the posterior or inferior medial wall. The suprapapillary portion of the duodenum was involved diffusely over a considerable extent in thirteen cases, the distal portion of the growth being situated near the papilla in ten, at the superior angle in two and in an indefinite location in one; the proximal margin of the growth was situated at the superior angle in four cases and in the bulbar region in nine. Neoplastic tissue was regularly found infiltrating the wall of the duodenum for varying distances, but in three cases the lesion was comparatively superficial (Herman and von Glahn and Dewis and Morse, cases 1 and 2). Opposite the primary growth a well defined tumor mass was often present on the peritoneum.

The primary growth was ulcerated in thirty instances and nonulcerated in eight, and no mention was made of this feature in three. The ulcers were round, oval or crater-like, and in the constricting lesions there were running ulcers. Their margins were thick, rolled, broad, elevated, papillated, everted or honeycombed, and either sharply defined or irregular. The base was described in only a few instances, as gray, smooth, nodular, hard or soft, and in one it was covered by greenish red material. A superficial thrombosed or ruptured blood vessel was noted in the base of the ulcer in three cases, and in two others perforation had occurred. The ulcerated lesions were generally annular and constricting but never completely obstructive in contrast to the nonulcerated type, in half of which the lesions were almost totally stenotic.

Extension or metastases were present in thirty-one cases. This is probably a conservative figure, for in several instances only the surgical specimen was examined, and in a few others autopsy was limited to the abdomen. Adhesions to the pancreas were mentioned in sixteen cases and were inflammatory, neoplastic or both. Inflammatory adhesions were associated with local ulceration and infection and probably facilitated extension of the neoplasm. Secondary deposits in the pancreas occasionally attained a large size, measuring 6 cm. in diameter. Gross appearances suggesting tumorous infiltration of the pancreas were not always confirmed histologically (Dewis and Morse, case 3, and Pacetto), whereas other tumor foci may be only microscopic in size.

Obstruction of the common bile duct was present in eleven cases, in most of which the duct was encircled by neoplastic extensions from the duodenal lesion. In Dardinski's case there were also a few small nodules in the mucous membrane of the common bile duct at the point of obstruction. Rutishauser's case 5 is sometimes cited (Willis) as an example of intracanalicular extension along the bile ducts, but from the gross description it is evidently only another example of periductal involvement. Direct infiltration of the hepatic and cystic ducts occurred in two cases. In another (Morrison and Feldman) the growth in the duodenum compressed the hepatic duct without actually invading it. Cholecystoduodenal adhesions were observed in eight cases and were dense and fibrous in all but one, in which they were fibrinous. They were proved by microscopic examination to contain neoplastic tissue only in our case 4. The falciform ligament was infiltrated with tumor tissue in three cases.

Implantation metastases occurred as discrete nodules in six cases in the mesentery, transverse colon, gastrohepatic omentum, under-surface of the diaphragm, small intestine, pelvic wall and ovary. Rutishauser's case 1 is unique in respect to the large number of implantation metastases, and the question naturally arises whether the three small duodenal lesions regarded by him as primary may not rather have been metastatic from an unidentified source. Primary carcinoma of the prostate and thyroid glands is sometimes responsible for tumor spreads of this type and extent, but these glands were not described in Rutishauser's communication.

Cancerous involvement of the regional lymph nodes was observed in sixteen cases, in four of which the nodes in the gastrohepatic omentum, around the bronchi and in the mesentery and around the aorta were also involved. Metastatic deposits were present in the liver in eighteen cases, in the lungs in one and in the fifth and eighth dorsal vertebrae in one.

Dilatation of the stomach was mentioned in twelve cases uncomplicated by gastro-enterostomy and is considerably less pronounced a

feature than in carcinoma of the infrapapillary portion of the duodenum. Of seven cases in which the contents of the stomach were described, blood was found in four and bile in one. The mucous membrane of the stomach was atrophic in four cases and hypertrophic in one; the absence of free hydrochloric acid in the contents of the stomach in one of the former group was attributed to the atrophic condition of the gastric mucous membrane. The bowel distal to the primary duodenal lesion was distended and filled with blood in a few cases.

Generalized peritonitis occurred in two cases as a result of perforation of the duodenum. Small bloody effusions into the peritoneal cavity were observed in three instances, in each of which metastatic lesions were present on the serosa.

A single diverticulum of the duodenum was found in two cases, and in each of these the neoplastic growth occupied the margins of the sac (Bibby and Stewart; Morrison and Feldman).

In four cases there was obstruction of the pancreatic ducts with dilatation of the proximal ducts and atrophy of the parenchyma. In eight others there was chronic pancreatitis, the result in part of drainage of infected material from ulcerated lesions in the duodenum. Some degree of chronic pancreatitis may have existed prior to the development of cancer in three patients who gave an antecedent history of chronic cholecystitis.

Chronic cholecystitis was present in ten cases, in nine of which there were associated gallstones, gravel being present in the common bile duct in one, while in another a marble-sized calculus was removed from the ampulla of Vater.

The liver and bile passages showed the characteristic changes of biliary stasis in the cases of obstructive jaundice. There were dilatation of the large biliary ducts, proliferation of the small ducts, fibrosis of the portal radicles, degeneration and pigmentation of the parenchyma in the inner portions of the lobules, focal mid-zonal and biliary necroses and, in three cases, hepatic abscesses and cholangeitis.

HISTOLOGY

All the cases were of the glandular type of carcinoma except one, which was of the adenosquamous variety. Acinous formation was present in thirty cases and absent in one, while it was not mentioned in ten. The acini were irregular in four cases and cystic in three; in four there was a papillary arrangement. The lesion was designated as mucinous carcinoma in three cases, and in several others considerable basophilic fibrillar material was present in and between the tumor cells and in the acini. The cells grew discretely in strands, nests or clumps in sixteen cases, in only one of which acinar structures were entirely absent. The

cells were essentially columnar or cylindric, although pleomorphism was occasionally marked, some cells being cuboidal, round, oval, polygonal or flat. Variation in size, shape and staining of the nuclei was also frequently noted, and of fourteen cases in which mitotic figures were observed they were numerous in nine and infrequent in five. The stroma, described in seventeen cases, was minimal in four and abundant in thirteen, the scirrhous character of the latter being an outstanding feature. Areas of hemorrhage and necrosis were often observed, and the connective tissue was regularly infiltrated with small round cells and occasionally with polymorphonuclear neutrophils and eosinophils. The inflammatory reaction was frequently intense about areas of ulceration and necrosis, and in one case there were multiple areas of suppuration. In Lageder's case the tumor varied considerably in the various sections, being almost entirely scirrhous in some and very cellular in others, forming acini occasionally with papillary projections, and in one section polymorphism was pronounced, hyperchromasia the rule and mitotic figures numerous. One section also showed a transformation into epidermoidal elements, with voluminous cells occurring singly and in groups of from ten to twenty or more to form large plaques, the centers of which showed fusion of cytoplasm and beginning keratinization.

Malignant transformation occurred at the margin of the ulcer in four cases and in the superficial and deeper portions of the mucosa in one case each, while in one subject the ulcerated surface was formed by muscle infiltrated by neoplastic cells, both edges of the ulcer presenting atypical glandular formation resembling somewhat the picture seen in chronic ulcer.

CLINICAL FEATURES

Onset.—The cases were divided on the basis of onset into three groups: acute onset, twenty-two; gradual onset, seventeen, and indefinite onset, two. This division was made irrespective of an antecedent history of symptoms referable to the upper portion of the abdomen, which was elicited in twelve of the cases in which the onset was acute and in four of the cases in which it was gradual.

In the cases in which the onset was acute there were many symptoms, chief among which were the following: vomiting (fourteen cases), epigastric pain (twelve), weakness and loss of weight (eleven), jaundice (six), anorexia (six), flatulence (five), belching (five), sense of pressure or weight in the epigastrium (four) and constipation (three). The duration of symptoms in eighteen of these cases ranged from one week to nine months, with an average of about three months. In three of the remaining four cases the onset occurred from three to six months before admission; the patients in two of these cases were not heard from after discharge from the hospital, and the patient in the other case died within

two years. In the other case, despite the fact that symptoms had existed for one and a half years, the onset was acute, due apparently to biliary obstruction by infiltrating carcinomatous tissue.

The duration of symptoms in the gradual group ranged from six months to four years, with an average of sixteen months. The early symptoms were pain (eleven cases), dyspepsia, heaviness or distress (eight), loss of weight (eight), vomiting (four), weakness (five), anorexia (four) and jaundice (two). An acute exacerbation or sudden change in symptomatology occurred in ten of these. The average duration of this later acute phase was two months, the clinical manifestations being vomiting (five cases), epigastric pain (five), jaundice (two) and constipation (two).

As mentioned previously, a history of antecedent illness was elicited in sixteen cases. The condition was described as disease of the biliary tract in five, gastric or duodenal ulcer in five, tuberculosis in one and indeterminate lesions of the upper part of the abdomen in six, in two of which pancreatitis and pericholecystic adhesions were demonstrated at autopsy. Of five cases with a history of disease of the biliary tract, a large duodenal diverticulum was present in one, while in the remaining four operation or autopsy revealed calculous cholecystitis.

The five cases in which duodenal or gastric ulcer was suspected were reported by Letulle, Jefferson, Ramond, Vincent and Clément, Kettle and Archibald. No conclusive evidence of the etiologic relationship between ulcer and carcinoma was advanced by these authors. In Jefferson's case posterior gastro-enterostomy was performed for relief of indigestion, epigastric pain and vomiting, and, according to the hospital records, an ordinary nonmalignant ulcer of the duodenum was found. Postoperative convalescence was satisfactory, and the patient continued in excellent health for two and a half years, when diarrhea and abdominal pain gradually developed, with loss of weight, and death occurred a year later. At autopsy a completely annular, almost totally obstructive carcinoma of the duodenum was found. In this case it seems reasonable to question the accuracy of the original diagnosis of simple ulcer, since no statement was made as to whether it was inspected directly by opening the duodenum, or whether biopsy was performed. Since obstructive phenomena were obviated by the procedure of gastro-enterostomy in this case, it is not improbable that the lesion was malignant from the onset.

Pain, Tenderness and Rigidity.—Pain was reported in twenty-eight cases, was absent in six and was questionable in three, while in the remaining four epigastric distress, soreness, a sense of pressure in the abdomen, heartburn or pain on deep palpation over the neoplasm were

the complaints. Of two patients who did not complain of pain, one was senile and the other was a morphine addict. Pain occurred early in the disease in seventeen cases and late in five, and it was likely to appear at any time of the day or night, lasting from a few minutes to several hours. It was present in the epigastrium in fifteen cases and in the lower portion of the abdomen in two and was generalized over the abdomen in one, radiating to the back in four and to the right loin and right shoulder in one each; in one case it was at first substernal and later radiated to the eleventh dorsal segment and the epigastric region. The pain was severe in six cases, intermittent or paroxysmal in nine, continuous in three and vague or variable in two. The ingestion of food preceded the onset of pain usually by from one-half to two hours in ten cases and gave symptomatic relief in two, while in three it had no effect. Abdominal tenderness was associated with pain in ten cases and was present without pain in two cases. All three patients with abdominal rigidity had pain, and one had abdominal tenderness. Pain was associated with vomiting and sour eructations in two cases, while in three others it was relieved by vomiting or belching or by the administration of alkali; in one case pain and other symptoms disappeared following cholecystectomy and choledochogastrostomy. No correlation could be established between the symptom of pain and the situation and size of the primary growth or adhesions to and neoplastic infiltrations of surrounding structures.

Vomiting.—Vomiting occurred in twenty-six cases, was absent in six and was not mentioned in nine. This symptom occurred in sixteen cases in which the onset was acute, in seven cases in which the onset was gradual at first and then became acute, in two cases in which the course was gradual throughout and in one case in which the onset was indefinite. Of the cases in which the onset was acute, vomiting was an early symptom in ten and developed later in six. Of the cases in which the onset was at first gradual and then acute, vomiting occurred with the gradual manifestations in only two and coincidentally with the acute manifestations in five. Of the cases in which the course was gradual throughout, vomiting was an early symptom in one and appeared later in another. Nausea and vomiting usually occurred together, the nausea appearing a week or so before vomiting commenced, the latter tending to become incessant terminally. Vomiting was initiated or exaggerated by food in nine cases, while in ten no such relationship was established. The vomitus contained blood in several instances, as well as particles of food which had been ingested from one to ten days previously and which sometimes exhibited evidences of putrefaction. Biliary vomiting was present in only one case in which the bile drained into the stomach

through a choledochogastrostomy opening, the operation having been performed early in the course of the disease.

Absence of vomiting was definitely stated in six instances. In the first of these the symptoms were not described in detail during an eight month interval between exploratory laparotomy and death. In another the dimensions of the primary lesion were not accurately stated. In a third the presence of a gastro-enterostomy opening obviated the effects of duodenal obstruction. In the other three cases the primary duodenal carcinoma was small, measuring, respectively, 0.6, 1.8 and 2 cm. in the greatest diameter. From this analysis it is evident that vomiting occurs regularly with the onset of intestinal obstruction but develops occasionally before there is any appreciable encroachment of the primary lesion on the lumen of the intestine. It is also possible that ulceration of the primary lesion may in some instances permit the passage of duodenal contents, and in such cases vomiting may be absent.

Jaundice.—Jaundice was present in seventeen cases, absent in fourteen and not mentioned in eight. It occurred with the acute symptoms in nine and from five to seven months after the onset in six, while in two its time of occurrence was not stated. It was due to neoplastic infiltration of the common bile duct in six cases, neoplastic obstruction of the hepatic duct in two, metastatic carcinoma of the head of the pancreas in one, pressure of the primary tumor and associated diverticulum in one and stone in the ampulla of Vater in two. In five cases the cause of jaundice was not accurately stated in the reports but was probably due to biliary obstruction. The location of the obstruction in the biliary tract depends to some extent on the segment of duodenum involved by the neoplasm; thus, in two cases in which the carcinoma originated near the pyloric orifice the hepatic ducts were obstructed, whereas neoplastic involvement of the lower end of the common bile duct was associated with tumors arising just above the papilla of Vater. Of the four cases with jaundice in which the duodenal growth was localized at the superior angle, biliary stasis resulted from neoplastic invasion of the common duct and hepatic duct (one case each), stone in the ampulla of Vater (one) and compression of the bile ducts by a combination of diverticulum and primary neoplastic lesion (one).

Jaundice was regularly associated with clay-colored stools and bilirubinuria and increased progressively in intensity unless surgical measures were instituted for its relief. In Mateer and Hartman's case the icterus index, estimated every second day for a period of two weeks, increased from 27 to 74, duodenal drainage on two occasions yielding no bile. Pain was present in eleven cases in which jaundice was present, in five there was no pain and in one this symptom was not mentioned.

Pain and jaundice occurred simultaneously in six cases, in two in association with cholelithiasis, and in five jaundice followed the appearance of pain.

Constipation and Diarrhea.—Constipation or obstipation occurred in fourteen cases and diarrhea in six cases, while in about 50 per cent the bowels were normal or there was no mention of abnormality. Constipation occurred with the onset in five cases and after the onset in three; of two cases in the former group, this symptom abated somewhat subsequently, being followed by diarrhea in one instance. Diarrhea, when it occurred, was usually persistent.

PHYSICAL EXAMINATION

A mass was palpated in the region of the primary tumor in ten cases, no evidence of a mass was detected in nineteen and there was no mention of this feature in the remainder. Although each of the following characteristics of the palpated mass was mentioned at least once, few details were available as to its size, shape, consistency, fixation, mobility, movement with respiration and continuity with liver dulness. In four cases there was associated tenderness.

It seemed of value to correlate the presence or absence of a palpable mass with the size of the local neoplasm and associated inflammatory lesions as demonstrated at autopsy. In doing this, the morbid anatomy of the condition was evaluated not so much in respect to the duodenum, pancreas, lymph nodes or serosa singly but rather in relation to the size of the lesions as a whole. For example, if the combined and associated neoplastic and inflammatory processes were extensive, the anatomic lesion was graded as large, even though the primary tumor in the duodenum was small. Of the ten cases in which a mass was palpated clinically, the anatomic lesion was graded as large in all but one. Of the cases in which a mass was not palpable or not mentioned clinically, the anatomic lesion was graded as large in sixteen cases and as small in fifteen. Local conditions may have interfered clinically with the palpation of a large anatomic lesion in seven cases, for in four there was a marked degree of rigidity or abdominal distention, in two the neoplasm was situated on the posterior wall of the duodenum and in the other there were dense local adhesions between the inferior margin of the liver and the anterior abdominal wall.

The liver or gallbladder or both were palpable in nine cases, in all of which obstructive jaundice was present. In one case the liver was enlarged and nodular and at autopsy showed metastatic nodules and biliary stasis. Dilatation of the stomach to the level of the umbilicus or symphysis pubis was noted in five cases, a succusion splash was heard in two and abdominal peristalsis was marked in three.

LABORATORY STUDIES

Analysis of the Gastric and Duodenal Contents.—Aspirated gastric contents or vomitus were examined in fourteen cases. Blood was present in eight instances and bile in one; in the latter choledochogastrostomy had been performed. Free hydrochloric acid was present in seven cases, absent in five and not mentioned in one; it was absent before and after a test meal in two, while in another it rose from 19 to 30 after this procedure. Total acidity ranged from 25 to 100 in ten cases, the average being 64. After a test meal the total acidity decreased from 87 to 45 in one case and rose from 34 to 49 in another. Duodenal drainage was carried out in only one case and yielded no bile on two attempts, the patient being jaundiced clinically; autopsy revealed obstruction of the common bile duct.

Stools.—The stools were examined in twenty-two cases, in fourteen of which blood was found either grossly or by chemical examination. The stools were acholic in nine cases, in all of which there was obstruction of the extrahepatic biliary passages. In eight additional cases of biliary obstruction, the stools contained large amounts of blood in four and were not examined in four. Typical "pancreatic" stools were found in only one case, in which the duct of Wirsung was obstructed and the duct of Santorini could not be found. In three others in which there was postmortem evidence of obstruction of the pancreatic ducts, the character of the stools was not described.

Blood Studies.—The red blood cell count or hemoglobin determination or both were reported in fourteen cases. These were normal in one case, in which, however, there was frequent vomiting, which may have produced some degree of hemoconcentration. In two cases hemoglobin estimations alone were reported and were below normal in each. In the remaining eleven cases there was marked anemia. In seven of these the color index was low, and in three it was high (1.01, 1.03 and 1.15). These findings contradict the opinion expressed by a number of authors that anemia is not a prominent feature in cases of duodenal cancer. The blood count may not be a true index of the degree of anemia, which may be masked by hemoconcentration due to dehydration incident to frequent vomiting. Loss of blood by hemorrhage occurs frequently, for blood was found in eight of fourteen specimens of gastric contents and in fourteen of twenty-two stools examined clinically; in several subjects extensive intestinal hemorrhage was demonstrated at autopsy.

Roentgenographic Examination.—The stomach and duodenum were examined roentgenographically after an opaque meal in eighteen cases, in eleven of which there was a demonstrable lesion. However, the true nature of the lesion was strongly suspected in only two cases (Mateer and Hartman, and Bastos), while in the remainder the following diag-

noses were made: ulcer (three cases), duodenal stenosis (two), carcinoma of the stomach (two) and adhesions and obstacle at the pylorus (one each). A filling defect was noted in the region of the pylorus in three cases and in the second portion of the duodenum in four, in one of which there was also a constant deformity of the duodenal cap, which was interpreted as due to displacement; in the remaining four cases no filling defect was described. The case reported by Herman and von Glahn demonstrated the value of comparing the roentgenograms with the morbid anatomic specimen. In this case the roentgenograms of the gastro-intestinal tract were reported as essentially normal, and although the length of the "stalk" of barium was commented on at the time, it was interpreted as the stream passing through the pylorus. Comparison with the postmortem specimen showed that the neoplasm had formed a canal through which the gastric contents passed, and this "stalk" represented the stream of barium passing through the lumen of the duodenal growth.

There were seven cases in which no lesion was demonstrated roentgenographically. In one case aggravated vomiting interfered with the examination, and in another there was considerable retention of food. The anatomic lesions present in the remaining five cases are described briefly. In Pacetto's case there was a firm fibrous ulcerated obstruction, measuring 4 cm. in length, which involved two thirds of the circumference of the first portion of the duodenum. In Meyer and Rosenberg's case the suprapapillary segment of the duodenum was greatly narrowed by an annular papillary mass extending from just beyond the pylorus almost to the papilla of Vater. McGuire and Cornish found an infiltrating mass at the lower border of the liver and connecting with the duodenum, but the dimensions and appearance of the lesion in the mucous membrane of the duodenum were not described. In Van Tienhoven's case there was an ulcerating "brussel sprout-like" lesion on the pyloric side of the papilla of Vater, which was entirely free of neoplastic tissue. In Oschner and Wilbur's case an irregular area of ulceration, measuring 4 by 1.5 cm., was found 3 cm. below the pylorus.

It has been emphasized by others that roentgenographic studies in cases of cancer of the suprapapillary portion of the duodenum are of considerable value from a negative standpoint. Thus in patients exhibiting signs and symptoms referable to the gastro-intestinal tract, such studies may rule out the possible presence of organic lesions of the stomach, colon or gallbladder. The difficulty of visualizing carcinoma in this region can be attributed to several important factors. For one thing, the distal two thirds of the duodenum empties rapidly and is usually not entirely filled at any one time. Furthermore, as a rule it is not possible to distinguish defects in the suprapapillary segment from

deformities due to ulcer. Even with obstruction of a relatively high grade associated with a large tumor, the only significant findings may be slight alteration in the mucosal patterns as outlined by remnants of the barium. Fixation and rigidity may be of some aid in excluding a diagnosis of benign tumor but are of no value in ruling out extrinsic cancers invading the duodenum from adjacent organs and structures such as the stomach, bile ducts, gallbladder, pancreas and lymph nodes. Gastric retention in the presence of a "vacuole" in the bulb may suggest

Results in Cases in Which Operation was Performed

Year	Author	Operation	Result
1905	Gerster	Cholecystectomy	Died 22 hr. after operation
1906	Geiser Case 1	Gastro-enterostomy; jejunostomy	Died 2 days after operation
1916	Jefferson	Gastro-enterostomy	Died 3½ yr. after operation
1920	McGuire and Cornish Case 3	Duodenostomy	Operative recovery; discharged
1921	Van Tienhoven Case 3	Cholecystogastrostomy	Operative recovery; discharged
1927	Morrison and Feldman	Exploratory	Operative recovery; died 7 mo. later
1928	Dewis and Morse Case 1	8/6/26: gastro-jejunostomy; 10/21/26: resection of pylorus and first portion of duodenum	Operative recovery; discharged
	Case 2	Excision	Operative recovery; discharged
	Case 4	Choledocholithotomy	Died 6 days after operation
	Case 5	Excision	Died 4 days after operation
1930	Archibald	Exploratory	Died 21 days after operation
1931	Pacetto	Gastro-jejunostomy	Died 5 days after operation
1932	Mateer and Hartman	Exploratory	Died 9 days after operation
1932	Rutishauser Case 5	Gastro-enterostomy	Died 3½ mo. after operation
1932	Cave Case 8	2/11/14: appendectomy; 7/6/14: cholecysto-enterostomy; 10/20/14: gastro-enterostomy	Died 3 mo. after operation
1933	Eger Case 1	12/24/31: gastro-enterostomy; 4/6/32: cholecystostomy	Died 10 mo. after operation
1934	Dardinski	Gastro-jejunostomy; cholecystostomy	Died 2 days after operation
1936	Stewart and Lieber Case 1	1/2/30: cholecystectomy, choledocholithotomy and choledochostomy; 4/4/30: choledochogastrostomy; 4/14/31: gastro-enterostomy	Died 3 days after operation

tumor but does not exclude a growth at the pylorus or prolapse of the gastric mucous membrane into the duodenum.

DIAGNOSIS

A correct preoperative clinical diagnosis was made in only two cases, and in these on the basis of the roentgenographic picture (Mateer and Hartman and Bastos). A clinical diagnosis of carcinoma of the stomach or pylorus was made in eight cases, of duodenal ulcer in two, and of intestinal obstruction in two, while the following diagnoses were mentioned once: malignant obstruction of the common bile duct, carcinoma, disease of the gallbladder, carcinoma of the gallbladder or pancreas,

acute indigestion, empyema of the gallbladder, tuberculous peritonitis, calculous cholecystitis, an inflammatory process of the duodenum and probable carcinoma of the duodenum with obstruction of the common bile duct. A correct diagnosis was made at operation in ten of eighteen cases; the other diagnoses were carcinoma of the pancreas (two cases), carcinoma of the pylorus (one), fibrous obstruction of the duodenum (one) and malignant obstruction at the ampulla of Vater (one); no diagnosis was recorded in three of the surgical cases. When gastroenterostomy is done early and the malignant character of the lesion is not suspected, the subsequent clinical improvement may be so marked that a correct diagnosis is deferred until the late stages of the condition.

Early accurate diagnosis of carcinoma of the suprapapillary portion of the duodenum depends largely on thorough evaluation of the symptom complex which antedates the onset of intestinal obstruction. These early symptoms consist of vague mild complaints present intermittently for months, characterized by dyspepsia, intermittent attacks of pain, abdominal discomfort, loss of appetite and loss of weight. A mass is rarely palpable at this stage of the disease, and the roentgenographic studies are of little direct help. Later the basic symptoms in the majority of cases are those referable to intestinal and biliary obstruction. It is probable that the lumen of the intestine is temporarily obstructed for a few hours or so, followed by relief for several hours, days, weeks or even months before another attack occurs. As the disease progresses, the clinical manifestations of obstruction recur more frequently until finally nausea and vomiting develop in the vast majority of the patients. The relative incidence of the various clinical symptoms and signs and laboratory findings has been discussed under their respective headings.

TREATMENT

Reports of roentgen and radium therapy have been presented by Levin and Bastos. The results of surgical intervention in the patients in this series have not been encouraging. No instance of definite cure has as yet been recorded. As indicated in the table, seven patients died shortly after operation and four others within six months; two survived a little over a year and one two years. The subsequent fate of four patients who survived operation and were discharged from the hospital is not known. Technical considerations of the surgical treatment of carcinoma of the duodenum have recently been described by Pack and Scharnagel and Whipple, Parsons and Mullins. The difficulties that are frequently encountered may be illustrated by the fact that in the majority of cases analyzed, the process was extensive, ulcerating and constricting and frequently involved adjacent structures. In the present series, the regional lymph nodes were invaded by metastases in sixteen

cases and the bile ducts in twelve, and there were either neoplastic or inflammatory adhesions to the pancreas in sixteen cases and to the gallbladder in eight. Obviously the measures to be employed in any individual case must depend on the condition of the patient, the character and extent of the lesion and the presence and degree of intestinal or biliary obstruction.

SUMMARY AND CONCLUSIONS

This study of carcinoma of the suprapapillary portion of the duodenum represents a clinical and pathologic correlation based on six new cases and thirty-five cases reported in the literature; references to sixty-eight additional cases reported as examples of this condition are listed.

One case was found in 3,526 autopsies (0.028 per cent) and four cases in 20,176 autopsies (0.019 per cent).

The average age was 55.75 years, twenty-four of the patients being men and fifteen women.

The onset was acute in 53.6 per cent of cases and gradual in 41.4 per cent, an antecedent history of symptoms referable to the upper portion of the abdomen being elicited in approximately half of the cases in which the onset was acute and in several in which it was gradual. The symptoms occurring most frequently in the cases in which the onset was acute were vomiting, epigastric pain, weakness, loss of weight and jaundice, and the average duration ot life was three and a half months. The early symptoms occurring most frequently in the cases in which the onset was gradual were abdominal pain, dyspepsia, loss of weight, vomiting and jaundice, and the average length of life after the onset was sixteen months. A marked change in symptomatology occurred in 62 per cent of the cases in which the onset was gradual, symptoms occurring which resembled those in the group in which the onset was acute. A mass was palpated clinically in the region of the primary tumor in approximately 24 per cent of the cases. The gastric or duodenal contents contained blood in eight of thirteen cases, free hydrochloric acid in seven, and bile in only one in which cholecystogastrostomy had been performed. The stools contained blood in thirteen of twenty-one cases, and nine were acholic; typical "pancreatic" stools were found in one case in which the duct of Wirsung was obstructed. A marked grade of anemia was present in ten cases, the color index being low in seven and high in three. Roentgenographic studies are of little direct value in making a positive diagnosis of carcinoma of the suprapapillary portion of the duodenum. In a few cases evidence of an ulcerated lesion in the duodenum or of obstruction of the gastro-intestinal tract was suggested but, on the other hand, extensive constricting lesions were frequently not demonstrated. Irrespective of the anatomic point of obstruction, the findings are frequently interpreted as pyloric obstruc-

tion. This method of examination is of greatest value in ruling out lesions of the stomach, colon or gallbladder.

A correct preoperative clinical diagnosis of carcinoma of the suprapapillary portion of the duodenum was made only twice. A correct surgical diagnosis was made in nine of seventeen cases, biopsy being of especial value in this connection. No instance of cure has been recorded, although follow-up studies were incomplete in a few cases.

The growth averaged 2.5 cm. in length in 56.1 per cent of cases and varied from 4.5 to 8 cm. in length in 31.7 per cent. It was localized in 68.3 per cent of cases, and in one half of these to the bulbar region. Ulceration occurred in about 73 per cent of cases, about half of these being annular or constricting lesions. Extension or metastasis occurred in 75.6 per cent of cases, to the liver, lymph nodes, pancreas, biliary passages, peritoneum, lungs and bone. All the growths were adenocarcinoma but one, which was an adenosquamous cell carcinoma.

No definite evidence has been advanced to support the hypothesis that simple ulcer of the duodenum is a precancerous lesion.

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CONCEALED HEMORRHAGE INTO TISSUES AND ITS RELATION TO TRAUMATIC SHOCK

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Evident hemorrhage, such as that from a cut vessel, with external bleeding has long been recognized as a factor of importance in traumatic shock. In certain instances during a surgical operation, when the blood is distributed on a large number of sponges, sheets and towels, the full extent of the hemorrhage is sometimes not realized. But at least it is recognized as being a factor of importance and is treated by methods intended to restore the loss of circulating fluid.

On the other hand, there are many instances in which the hemorrhage is hidden and not recognized. The shocklike symptoms that develop in patients so affected are attributed to the action of a variety of ill defined agents, such as the toxic action of traumatized tissue, anociassociation, etc. The exact relationship between the cause and the condition being indirect and uncertain, the treatment is equally indefinite. It is with the intention of showing that some of these patients suffer from hidden hemorrhage sufficient to account for their symptoms that this paper is written. Such hidden hemorrhage may be either (1) into a body cavity, such as the pleural or peritoneal cavity, or into a hollow organ, or (2) into the tissues. The first type is generally recognized as being of importance and is overlooked usually because of inability or failure to make an adequate physical examination. The second type of hidden hemorrhage is allowed to pass unrecognized in most clinical cases because its importance is not generally realized.

In experimental work on traumatic shock it was only recently that the full importance of hidden hemorrhage and extravasation of plasma into the tissues was recognized. Bayliss and Cannon [1] in 1919 performed experiments on cats wherein one hindleg was severely traumatized and the other left as a control. After death of the animal the two legs were amputated and the weights compared. There was not enough difference in weight to attribute death to hemorrhage into the tissues. Later observers, however, including Phemister,[2] Blalock [3] and Parsons and

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1. Bayliss and Cannon, cited by Parsons and Phemister.[4]

2. Phemister, D. B.: The Vascular Properties of Traumatized and Laked Bloods and of Blood from Traumatized Limbs, Ann. Surg. **87**:806-810 (June) 1928.

3. Blalock, A.: Experimental Shock: The Cause of the Low Blood Pressure Produced by Muscle Injury, Arch. Surg. **20**:959-996 (June) 1930.

Phemister,[4] repeated the experiments of Bayliss and Cannon but amputated the traumatized limb at a higher level, so as to include the loose tissue spaces of the inguinal region into which much of the extravasated blood and plasma had diffused. The difference in weight between the two hindlimbs was found by Parsons and Phemister sometimes to be as much as 60 per cent of the total volume of blood.

Division of the caudal portion of the animal into two hindquarters and variants of this method were used by other authors to demonstrate the importance of local loss of blood and plasma in other types of shock. Loss of nearly whole blood occurs in shock due to trauma to an extremity, in portal obstruction (Elman and Cole [5]) and in intestinal strangulation (Scott and Wangensteen [6]). Loss of plasma-like fluid occurs in burns (Blalock,[7] Underhill [8] and Harkins [9]), in freezing

4. Parsons, Eloise, and Phemister, D. B.: Hemorrhage and "Shock" in Traumatized Limbs, Surg., Gynec. & Obst. **51**:196-207 (Aug.) 1930.

5. Elman, Robert, and Cole, Warren H.: Hemorrhage and Shock as Causes of Death Following Acute Portal Obstruction, Arch. Surg. **28**:1166-1175 (June) 1934.

6. Scott, H. G., and Wangensteen, O. H.: Blood Pressure Changes Correlated with Time, Length, and Type of Intestinal Strangulation in Dogs, Proc. Soc. Exper. Biol. & Med. **29**:428-431 (Jan.) 1932; Blood Losses in Experimental Intestinal Strangulations and Their Relationship to Degree of Shock and Death, ibid. **29**:748-751 (March) 1932.

7. Blalock, Alfred: Experimental Shock: VIII. The Importance of the Local Loss of Fluid in the Production of the Low Blood Pressure After Burns, Arch. Surg. **22**:610-616 (April) 1931.

8. Underhill, F. P.; Kapsinow, Robert, and Fisk, M. E.: Studies on the Mechanism of Water Exchange in the Animal Organism: I. The Nature and Effects of Superficial Burns, Am. J. Physiol. **95**:302-314 (Nov.) 1930; II. Changes in Capillary Permeability Induced by a Superficial Burn, ibid. **95**:315-324 (Nov.) 1930. Underhill, F. P.; Fisk, M. E., and Kapsinow, R.: III. The Extent of Edema Fluid Formation Induced by a Superficial Burn, ibid. **95**:325-329 (Nov.) 1930. Underhill, F. P., and Fisk, M. E.: IV. The Composition of Edema Fluid Resulting from a Superficial Burn, ibid. **95**:330-333 (Nov.) 1930. Underhill, F. P.; Fisk, M. E., and Kapsinow, R.: V. The Relationship of the Blood Chlorides to the Chlorides of Edema Fluid Produced by a Superficial Burn, ibid. **95**:334-338 (Nov.) 1930; VI. The Composition of Tissues Under the Influence of a Superficial Burn, ibid. **95**:339-347 (Nov.) 1930. Underhill, F. P., and Fisk, M. E.: VII. An Investigation of Dehydration Produced by Various Means, ibid. **95**:348-363 (Nov.) 1930; VIII. A Study of Dehydration by Pilocarpine Under Varied Dietary Conditions, ibid. **95**:348-370 (Nov.) 1930.

9. Harkins, H. N.: Shift of Body Fluids in Severe Burns, Proc. Soc. Exper. Biol. & Med. **31**:994-995 (May) 1934; Experimental Burns: I. The Rate of Fluid Shift and Its Relation to the Onset of Shock in Severe Burns, Arch. Surg. **31**:71-85 (July) 1935; The Bleeding Volume in Severe Burns, Ann. Surg. **102**: 444-454 (Sept.) 1935.

(Harkins, Harmon and Hudson[10]), in intestinal trauma (Johnson and Blalock,[11] and Roome, Keith and Phemister[12]) and in peritoneal irrigation by hypertonic solutions (Domenech-Alsina and co-workers[13]).

REPORT OF CASES

In all cases of wounds and trauma there is some swelling. Hemorrhage occurs in some and only edema in others. In some instances this swelling may be marked and may be a vital factor. The following cases are intended to illustrate the importance of quantitative studies of the amount of swelling after trauma. The fluid present in these swellings contains a higher percentage of proteins than ordinary edema fluid, and hence its loss may lead to circulatory disturbance.

CASE 1.—Mrs. C. O'M., aged 46, had been in the hospital for three days because of a neurosis, when on March 9, 1935, at some time between 3:10 and 4 a. m., when found, she jumped out of a fourth story window, landing on a wood porch floor, a distance of 39 feet. The outdoor temperature was 27 F. at the time, and she was clad in only a thin nightgown. She was found unconscious, with a small amount of bleeding due to a laceration of the scalp. Her pulse was unobtainable, she was cyanotic and moaning and the blood pressure was not obtained for an hour and a half, when it was 60 systolic and 35 diastolic. She was given 1,800 cc. of saline solution intravenously followed by 500 cc. of blood. By 8 a. m. she was conscious, and the blood pressure had risen to 84 systolic and 40 diastolic, as shown in figure 1, but by noon it had fallen to 46 systolic, and there was a moderate cold perspiration over the upper half of the body. The red cell counts are shown in figure 1. Just before a second transfusion of 500 cc. of blood was given at 2 p. m. the count was 3,800,000. The pulse rate for two days before the accident averaged 120 (basal metabolic rate, plus 11). It ranged from 140 to 160 the first five days after the accident, and then it came down gradually to 110. The laceration of the scalp was sutured soon after the patient was discovered, and two days later roentgenographic studies revealed fractures of both innominate bones, the right ninth rib, the left radius, the right greater trochanter of the femur and the left clavicle. There were extensive ecchymoses and swellings of the right side of the chest, the right side of the abdomen and the right

10. Harkins, H. N.: Shock Due to Freezing: I. Shift of Body Fluids and Associated Blood Concentration Changes, Proc. Soc. Exper. Biol. & Med. **32**:432-434, 1934. Harkins, H. N., and Hudson, J. E.: Shock Due to Freezing: II. Composition of Edema Fluid, ibid. **32**:434-435, 1934. Harkins, H. N., and Harmon, P. H.: Experimental Freezing: Bleeding Volume, General and Local Temperature Changes, ibid. **33**:1142-1143, 1935.

11. Johnson, G. S., and Blalock, Alfred: Experimental Shock: XII. A Study of the Effects of Hemorrhage, of Trauma to Muscles, of Trauma to the Intestines and of Histamine on the Cardiac Output and on Blood Pressure of Dogs, Arch. Surg. **23**:855-863 (Nov.) 1931.

12. Roome, N. W.; Keith, W. S., and Phemister, D. B.: Experimental Shock: The Effect of Bleeding After Reduction of the Blood Pressure by Various Methods, Surg., Gynec. & Obst. **56**:161-168 (Feb.) 1933.

13. Domenech-Alsina, F.; Benaiges, B., and Arqué, P.: Etude du choc provoqué par l'irrigation péritonéale hypertonique, Compt. rend. Soc. de biol. **114**: 104-105 (Feb. 12) 1933.

arm and leg. Measurements of the right side of the body were compared with those of the left side and are shown in table 1. The maximum amount of swelling was about 1,550 cc. It is to be remembered that the left side of the body may have swelled in certain places, and there may have been some hemorrhage into the thoracic and abdominal cavities not determinable by physical examination. Furthermore, as the interval between the time the patient was last seen in her

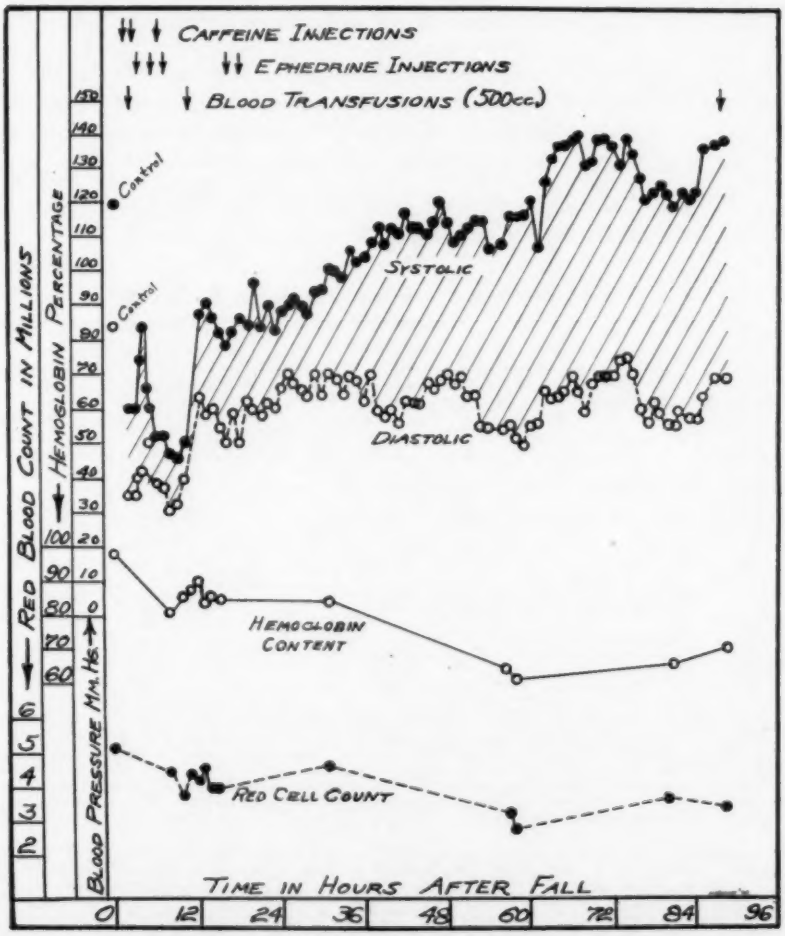

Fig. 1 (case 1).—Chart showing the course of blood pressure and blood concentration after traumatic shock associated with multiple fractures and local swelling. Injections of epinephrine hydrochloride administered subcutaneously and 1,800 cc. of physiologic solution of sodium chloride administered intravenously were given at the same time as the first injection of caffeine sodiobenzoate. The prolonged lowering of blood pressure over a period of forty-eight hours with recovery is of interest.

room and that when she was found on the porch floor amounted to fifty minutes, the effects of exposure to cold have to be considered. The first comparative

measurements were recorded twelve hours after the accident. Other readings taken almost daily during the next two weeks showed no further swelling. Nine days after the accident the asymmetry began to disappear; in twelve days it had almost disappeared, and two weeks after the injury measurements on the two sides were about equal. The measurements were taken at different points, and the volume was calculated for each segment as that of a frustum of a cone. A rough estimate of volume is thus derived from the well known formula:

$$V = 1/3\,\pi\,h\,(r_1^2 + r_2^2 + r_1 r_2)$$

In this patient the steady fall in the red cell count despite the absence of continued external hemorrhage and of known hemorrhage into the visceral or body cavities is of interest. Continued hemorrhage into the injured tissue spaces may have been a factor. Restoration of the blood volume by an inflow of fluid from the noninjured tissues in remote parts of the body is another possible cause.

TABLE 1.—*Measurements of Arms, Leg and Body in Case 1* *

	Right Side		Left Side	
Point of Measurement	Circumference, Cm.	Volume, Cc.	Circumference, Cm.	Volume, Cc.
5 cm. above elbow	29.0	308	28.5	292
Elbow	26.5	270	25.5	244
5 cm. below elbow	25.5		24.0	
22 cm. above patella	50.5	2,390	55.5	2,070
12 cm. above patella	49.5	3,000	46.0	2,730
12 cm. below patella	30.5		29.5	
Semicircumference of abdomen	42.0	5,605	39.0	4,845
Total		11,633		10,181
Excess		1,552		

* The excess volume of the right arm is inappreciable, while that of the right leg and the right side of the body is considerable. It is not known, however, that the opposite limbs or portion of the abdomen were of normal size. The volume of the halves of the abdomen is calculated as that of a half of a cylinder with the semicircumference given, and a length of 20 cm., that is, approximately the extent of the ecchymotic region on the right side. The excess of 1,550 cc., if composed of blood or plasma, would be a factor of importance in the production of traumatic shock.

CASE 2.—Mrs. C. L., aged 42, received fractures of the left femur, left tibia and both bones of the left forearm just before admission to the hospital. The volume of about two thirds of the left thigh was 8,900 cc. by measurement and of a corresponding portion of the right thigh 7,100 cc., representing a swelling of 1,800 cc. However, since there was 1.5 cm. shortening of the thigh due to fracture, using the average circumference of the thigh as 50 cm., the corrected swelling was 300 cc. less, or about 1,500 cc. This did not include the swelling of the arm or tibial region. A good portion of this swelling was present within a few hours after the injury; it was somewhat more marked in three days and had absorbed to some extent in ten days.

The blood pressure was 94 systolic and 68 diastolic two hours after the patient's admission, and she was given a transfusion of 650 cc. of blood immediately and a similar transfusion four days later. The red cell count was 3,900,000, the hemo-

globin content 70 per cent (Sahli) and the hematocrit reading 34 on the day of admission (after a blood transfusion). The red cell count two days later was 2,600,000 and gradually rose thereafter.

Case 3.—Mrs. J. L., aged 51, entered the hospital an hour and a half after a severe automobile accident with fractures of the shaft of the left femur, the right tibia and the fibula in two places (the upper and the lower third), both bones of the right forearm, the right innominate bone, a 3 inch incised wound of the scalp and a jagged 5 inch incised wound of the wall of the lower part of the abdomen. The amount of hemorrhage from the external wounds had been relatively small, while there was great swelling around the sites of the fractures. These swellings were not measured. There were no specific signs of fat embolism. The blood pressure on admission was 60 systolic and 40 diastolic, and after the administration of 1,500 cc. of Ringer's solution intravenously, it rose to 114 systolic and 74 diastolic five hours after the accident. It remained around 120 systolic until forty-eight hours after the accident, when it fell to 98 diastolic and 60 systolic. Transfusion of 500 cc. of blood restored it to normal, where it remained. The

Table 2.—*Changes in the Blood Concentration in Case 3*

Time	Hemoglobin Content	Red Cell Count, Millions
On admission	93	5.2
14 hours later	85	4.3
18 hours later	60	3.4
36 hours later	..	3.7
48 hours later	55	2.9
50 hours later	Blood transfusion, 500 cc.	
60 hours later	60	3.2
64 hours later	58	2.9
84 hours later	60	3.5
108 hours later	60	3.9
160 hours later	68	4.2

hemoglobin content and the red cell count fell steadily over the forty-eight hour period before the blood transfusion, despite the fact that all external hemorrhage was controlled, and there was no demonstrable hemorrhage into the body cavities or viscera.

Continued hemorrhage into the tissues at the sites of injury on the one hand and secondary effects of restoration of blood volume by inflow of tissue fluids at places remote from the injuries on the other hand are possible explanations of this continued dilution of blood just as in case 1. The blood changes are shown in table 2. Technical errors in determination of the hemoglobin percentage and red cell count undoubtedly account for some of the minor variations.

Case 4.—Mrs. C. S., aged 58, was admitted to the hospital with multiple fractures, a blood pressure of 50 systolic and 40 diastolic and the typical picture of traumatic shock following an automobile accident.[14] Despite blood transfusion and the administration of other fluid intravenously, she died eight hours after admission. Necropsy revealed a loss of about 1,200 cc. of blood at the site of

14. This case has previously been reported in full by Wilson, H., and Roome, N. W.: Am. J. Surg. **22**:333-334 (Nov.) 1933.

numerous fractures and from traumatic rupture of the aorta. In this case the concealed hemorrhage was partly into the tissues and partly into the pleural cavity and the mediastinum.

CASE 5.—Mr. J. P., aged 34, underwent a disarticulation of the hip for chronic osteomyelitis of the femur and suppurative gonitis on June 5, 1935, with a blood pressure reaction (fall to 96 systolic and 78 diastolic an hour after operation with prompt recovery). Twelve days later the patient became much worse, and it was found that he had bled about 1,000 cc. into the amputation stump. The blood pressure had again fallen to 98 systolic and 52 diastolic. He was given two blood transfusions totaling 1,000 cc. that day, with a rise in pressure to 105 systolic and 74 diastolic and eventual recovery. Marked edema involving especially the face disappeared soon after the transfusions and may have been due to a low level of plasma protein.

CASE 6.—Mrs. C. M., aged 30, caught her right hand and the lower half of the forearm under a folding sofa. Because she was alone in the house, it was five

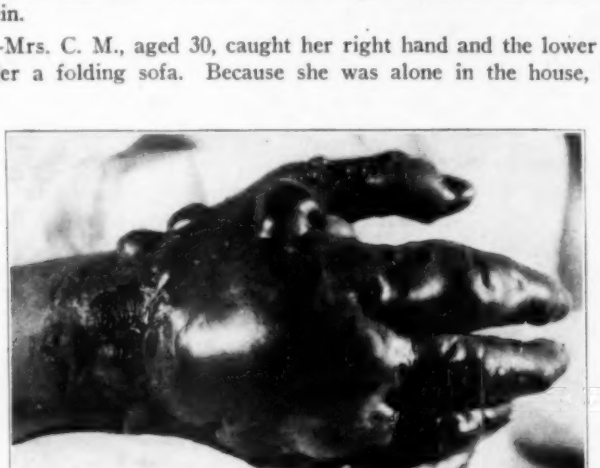

Fig. 2 (case 6).—Extreme swelling of hand of patient C. M. taken eighteen hours after the accident.

hours before she could be released. On admission to the hospital soon after, the hand appeared as shown in figure 2 with huge blisters. The blister fluid contained amounts of nonprotein nitrogen and sodium chloride similar to the composition of blood plasma, and it clotted spontaneously. The volume of the hand and forearm, as measured by a plethysmograph twelve hours after admission, was 600 cc. greater than the volume of the left hand and forearm. The red cell count at that time was 7,100,000, and the hemoglobin content was 95. The next day the red cell count was 6,600,000, and five days after admission it was 4,700,000. The blood pressure remained normal throughout. It seems unlikely that this amount of swelling could have produced all the blood concentration.

CASES 7-10.—These four cases represent instances of minor injuries in which quantitative measurement of the resultant swelling was made. In none of them was the trauma sufficient to cause shock, a fall in blood pressure or changes in the concentration of blood. Jack F., aged 4 years, had an increase in the size of the left thigh (measurement) of 200 cc. six hours after receiving a fracture of the left femur. Mrs. J. M. and Mrs. F. W. each ran her left arm through a wringer almost to the elbow. The first patient had a swelling of 260 cc. (measurement)

and 300 cc. (plethysmograph) and the second patient of 250 cc. (measurement). The readings in both instances were taken twelve hours after the injury. Two hours after a fracture of both bones of the right leg, Mrs. McM. had a swelling of 300 cc. (measurement) of the affected leg.

COMMENT

In some of the cases reported here concealed hemorrhage into tissues followed injury of such a slight degree that the loss of blood was not great enough to lead to shock. In only one case (case 4) did death result, and in this instance there was in addition bleeding into a body cavity and external bleeding. However, the lesson learned from the minor injuries of the group, namely, that there may be considerable loss of blood into the tissues which is not visible on casual examination, can be applied to more serious injuries. If a simple crushing of the hand and forearm can produce an increase in the local volume of several hundred cubic centimeters in a few hours, more extensive body injuries could easily produce a change of several times that much.

The measurements of circumferences of the limbs and body and subsequent calculation of the difference in volume on the two sides from the volumes of a series of frusta of cones is not expected to be an exact quantitative method. However, check measurements usually agreed quite well, and the volumes calculated were in all instances greater on the injured side. In one case a check reading was made by the plethysmographic method which agreed well with the calculated volume difference. In another instance only the plethysmographic reading was taken.

In most instances the swelling appeared rapidly in the first few hours after injury. After reaching a maximum, it took several days to subside. The relative abounts of extravasated blood and plasma constituting the swelling was variable with the injury, but as no incisions into the swollen areas were made or analyses performed, the exact proportions were uncertain. Local discoloration and lack of marked blood concentration would indicate that in those cases at least a good share of the swelling was due to a loss of whole blood.

This proportionate loss of whole blood and plasma in certain traumatic forms of secondary shock has led to some confusion in the literature. Coonse, Foisie, Robertson and Aufranc [15] stated that traumatic shock is accompanied by blood concentration and hemorrhagic shock by anemia. Moon [16] cited the same differentiating point between the two

15. Coonse, G. K.; Foisie, P. S.; Robertson, H. F., and Aufranc, O. E.: Traumatic and Hemorrhagic Shock: Experimental and Clinical Study, New England J. Med. **212**:647-663 (April 11) 1935.

16. Moon, V. H.: The Shock Syndrome in Medicine and Surgery, Ann. Int. Med. **8**:1633-1648 (June) 1935.

types of shock. It is probable that the time element alone is one of the chief factors differentiating the two types. In acute hemorrhage the loss of blood is sudden in many instances, and at death what Moon calls a "dry necropsy" is found, the tissues being anemic. With a slow leak of of blood into the tissues, the blood pressure is maintained at a low level for a prolonged period of time (as in case 1). This prolonged lowering of the blood pressure alone will give rise to increased permeability of capillaries and to certain organic changes typical of Moon's "wet necropsy" that he says accompanies shock. Even Coonse and his collaborators [15] admitted that slow hemorrhage simulates traumatic shock. In many types of shock, furthermore, especially after burns or experimental intestinal manipulation, the loss of fluid is almost entirely blood plasma, and naturally hemoconcentration results. In other types of shock, such as after physical trauma to an extremity, both whole blood and plasma may be lost, and at the other end of the scale stands simple hemorrhage in which only whole blood is lost. Consider for the minute a hypothetic closed vascular system containing 5 liters of blood and with a hematocrit reading of 50 per cent: 1. If 2 liters of plasma is lost the relation will be 2,500 cc. cells and 500 cc. of plasma, and the hematocrit reading will rise to 83; later, if tissue fluids restore this loss of fluid, the hematocrit reading will again drop to 50. 2. If 1 liter of whole blood and 1 liter of plasma are lost, the relation will be 2,000 cc. cells and 1,000 cc. of plasma, and the hematocrit reading will be 67. With varying proportions of loss of whole blood and plasma, the hematocrit reading will approach normal. In actual practice, it may be below normal, and a relative anemia will result due to inflow of tissue fluids. 3. Finally, if whole blood is lost, there is no change in the hematocrit reading in a hypothetic closed system, but the accompanying inflow of tissue fluids will theoretically always produce anemia. Elman, Weiner and Cole [17] have shown experimentally that with local anesthesia hemorrhage produces anemia but that with amytal anesthesia there may even be concentration of the blood after hemorrhage. Blalock [3] concluded his discussion of this aspect of the question by saying that "there may be two types of hemorrhage, that outside the body . . . and that into the tissues."

Concerning Crile's [18] report of slight change or leukopenia in shock and leukocytosis in hemorrhage, in several of the cases presented in

17. Elman, R.; Weiner, D. O., and Cole, W. H.: Effects of a General Anesthetic (Sodium Amytal) on the Erythrocyte Count Following Hemorrhage, Proc. Soc. Exper. Biol. & Med. **32**:793-796, 1935.

18. Crile, G. W., cited by Orr, T. G.: Hemorrhage and Traumatic Shock, in Lewis, Dean: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1935, vol. 1, chap. 9, p. 2.

this paper marked leukocytosis developed after injury; for example, case 1, 33,000; case 2, 19,000; case 3, 28,000, and case 4, 28,000.

SUMMARY AND CONCLUSIONS

External hemorrhage has long been recognized as producing secondary surgical shock; concealed hemorrhage into the body cavities and hollow organs has been recognized but is often not diagnosed, while concealed hemorrhage into tissue spaces has not been universally considered as an important clinical cause of secondary shock.

Cases of concealed hemorrhage and extravasation of plasma into tissue spaces are presented. The resultant swelling is usually greater when measured quantitatively than casual physical examination would have led one to believe.

The extensive concealed hemorrhage and plasma extravasation in clinical cases substantiates the experimental observations of others that such local loss of fluid from the circulating blood stream is a factor of importance in the production of secondary surgical or traumatic shock.

IODINE CONTENT OF BLOOD IN CHOLECYSTIC DISEASE

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That normal human blood contains iodine is a matter of rather recent observation, although its presence has been suspected for many years. One of the earliest treatments for goiter was with burnt sponge, and when early in the nineteenth century it was demonstrated that sponges are rich in iodine, the employment of this drug in the therapy of goiter came about inevitably. It was in 1820 that the Swiss physician, Coindet,[1] made this clinical application. From that day to this, iodine has been the standard pharmaceutic weapon against all forms of depletion of the thyroid gland.

Yet three quarters of a century elapsed before it was discovered that the thyroid gland is itself an iodine factory. The iodine content of the normal thyroid gland was demonstrated by Baumann[2] in 1895, and this discovery led chemists and biologists to endeavor to find out if iodine existed in other body tissues, though for many years thereafter the thyroid gland and its diseases formed the center of interest. In the United States public health workers and even agricultural chemists became intensely interested in the question of iodine deficiency and the normal distribution of iodine in living tissues. Working with domestic animals, David Marine and his colleagues determined the iodine content of the thyroid glands of different species, confirming Baumann's earlier assertion that the pathologic thyroid gland always has a low iodine content. Other investigators, among whom may be mentioned Cameron, Forbes, Fenger and McClendon, made many estimations of the amount of iodine contained in such materials as food and drinking water.[3]

There remained, however, the constant difficulty of making accurate estimations, because no method had been developed sufficiently delicate

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From the Department of Surgery, the DeCourcy Clinic.

1. Coindet, J. F.: Découverte d'une nouveau remède contre le goître, Ann. de chim. et phys. **15**:49, 1820.

2. Baumann, E.: Ueber das normale Vorkommen von Jod im Thierkörper, Ztschr. f. physiol. Chem. **21**:319, 1895.

3. Orr, J. B., and Leitch, Isabella: Iodine in Nutrition, Medical Research Council, Special Report Series, no. 123, London, His Majesty's Stationery Office, 1929.

to determine the minute quantities of iodine which are normal to most plant and animal cellular structures. This was especially true of the iodine content of blood.

DETERMINATION OF THE IODINE CONTENT OF BLOOD

When in 1922 the Swiss Goiter Commission, recognizing this need, requested the government bureau of hygiene to attempt the production of a better method, von Fellenberg,[4] of the bureau's personnel, was set to work on the problem. He succeeded in perfecting "a true micro-method for the determination of iodine," the lower limits of which were about one ten thousandth of a milligram (0.0001 mg.).

Among von Fellenberg's associates at Bern, where the experiments were conducted, was Sturm,[5] a Bavarian. After learning von Fellenberg's method, he returned to Veil's clinic at Munich, where he made numerous studies not only on the blood of patients with goiter (in whom he was primarily interested) but likewise on the blood of normal persons and of persons ill with diseases other than those involving the thyroid gland. Another student of von Fellenberg, Lunde,[6] of Oslo, Norway, further developed the master's method and in his own country studied the iodine content of the blood in normal and in thyrotoxic persons. Sturm's study was really the first noteworthy contribution on the subject of iodine values in human blood. Kendall and Richardson,[7] whom Orr and Leitch [8] credit with having presented "the first modern figure for blood iodine," had employed ox blood for most of their determinations, although a few samples of human blood had been tested prior to 1920.

The work was soon greatly extended, and determinations were made of the iodine content of the blood in many other diseases besides those of the thyroid gland. Factors influencing the results, the existence of which had been previously ignored, such as geographic location and season of the year, were now taken into consideration, and the results were judged accordingly. Thus Curtis and his collaborators [8] found:

> The average normal iodine content of human blood in Chicago is about 12γ per hundred cubic centimeters. This level falls during the winter months. It is

4. von Fellenberg, T.: Das Vorkommen der Kreislauf und der Stoffwechsel des Jods, Ergebn. d. Physiol. **25**:176, 1926.

5. Veil, W. H., and Sturm, A.: Beiträge zur Kenntnis des Jodstoffwechsels, Deutsches Arch. f. klin. Med. **147**:166, 1925.

6. Lunde, G.; Closs, K., and Pedersen, O. C.: Untersuchungen über den Blutjodspiegel bei der primären Thyreotoxikose, Biochem. Ztschr. **206**:261, 1925.

7. Kendall, E. C., and Richardson, F. S.: Determination of Iodine in Blood and in Animal Tissues, J. Biol. Chem. **43**:161, 1920.

8. Curtis, G. M.; Davis, C. B., and Phillips, F. J.: Significance of Iodine Content of Human Blood, J. A. M. A. **101**:901 (Sept. 16) 1933.

elevated during early menstruation and pregnancy. It is higher if the person is taking iodized salt regularly. In fact, many observations show that it is elevated by any form of iodine medication that has thus far been studied. Owing to the minute amount of iodine normally present within the blood, a special term of designation has been widely adopted. This, a gamma (γ) or microgram, is 0.001 mg. Thus, 100 cc. of human blood normally contains 0.012 mg. of iodine. The total iodine contained in the entire human blood stream is consequently less than 1 mg.

These same investigators, whose work was done at the Billings Hospital, Chicago, made observations on patients in that institution suffering from diseases other than those of the thyroid gland and also on normal, healthy members of the hospital staff. "The majority of hospital patients present a normal blood iodine," they wrote. "Among the diseases investigated were tuberculosis, chronic osteomyelitis, fractures, and Hodgkin's disease. The blood iodine is normal in patients with cancer. There are, however, two striking exceptions. In acute severe infections, as in septicemia, the blood iodine is elevated. It is likewise elevated in lymphatic leukemia." They concluded that the level of the iodine in the blood is controlled by the activity of the thyroid gland, and in disease of the gland, at least, the significance of the iodine content "is similar to that of the blood sugar in diabetes mellitus, and to that of blood calcium in parathyroid disease."

Yet as late as 1931, Orr,[9] who had spent a considerable time in the investigation of all methods then extant, remarked rather sadly:

It has been made clear that the present methods in use for the estimation of iodine in very minute quantities and in the presence of organic materials are so unsatisfactory as to impede further progress in research. There is need for a standard method of estimation, suitable for use by all workers alike, that will give results closely approximating to accuracy, or results in which the standard error is constant and known.

Notwithstanding these difficulties, the importance of estimating the iodine content of the blood was more and more impressed on those members of the medical profession who had to deal with diseases of the thyroid gland. The need was particularly felt in the so-called "goiter belt" in the Eastern Central portion of the country. After 1923, when von Fellenberg's method—a great improvement on any previously tried—was introduced, more progress became possible. Other ways of estimating small iodine contents were put forward by Leitch and Henderson[10] and by McClendon.[11]

9. Orr, J. B.: Iodine Supply and the Incidence of Endemic Goitre, Medical Research Council, Special Report Series, no. 154, London, His Majesty's Stationery Office, 1931.

10. Leitch, I., and Henderson, J. M.: Estimation of Iodine in Foodstuffs and Body Fluids, Biochem. J. **20**:1003, 1926.

11. McClendon, J. F.: The Determination of Traces of Iodine, J. Am. Chem. Soc. **50**:1093, 1928.

Late in 1932 Davis and Curtis [12] made use of the fact discovered by Winkler in 1916—that an iodide may be readily oxidized to an iodate. Using bromine for this oxidation, they were able to make quantitative determinations on the iodine content of the blood far more exact than any previously obtained. But as they admitted, the method "is by no means an easy one," requiring "experience and practice to obtain satisfactory results." The estimation of the iodine content of blood remains, therefore, a procedure which is not carried out as often as it might be for the good of the individual patient as well as for the orderly progress of an interesting and clinically valuable branch of medical science.

IODINE CONTENT OF BLOOD IN DISEASES OF THE GALLBLADDER

With the establishment of relatively simple and accurate means of determining the iodine content of blood, therapeutists were able to make practical clinical use of this valuable addition to their diagnostic equipment. Confined almost exclusively at first to disturbances of the thyroid gland, the value of determinations of the iodine content of blood in other disease conditions was soon demonstrated. For the past year and a half my associates and I have been making routine studies of the iodine content at the DeCourcy Clinic. Employed originally only in connection with goiter work, in endeavoring to arrive at a normal standard for the geographic area within a hundred miles of Cincinnati, we made more than two hundred determinations on the blood of patients suffering from other diseases as well.

In the course of these routine tests we found that the iodine content of the blood is markedly increased in cases of cholecystic disease of long standing and in cases of hepatic deficiency. We later found that in cases of acute cholecystitis there is always a high iodine content. After we had determined the normal to be from 3 to 6 micrograms per hundred cubic centimeters of blood, the following figures were obtained as an average in cases of disturbances of the liver and gallbladder:

Chronic cholecystitis with stones (20 cases)	16.6 micrograms
Hydrops of the gallbladder (4 cases)	13.6 micrograms
Carcinoma of the liver (3 cases)	650.00 micrograms
Chronic cholecystitis (stone in the common duct) (5 cases)	2,090.00 micrograms

In cases of chronic cholelithiasis the figure before the administration of dextrose was 110 micrograms. After the administration of 1,500 cc. of 5 per cent solution of dextrose the figure fell to 86.7 micrograms. All determinations were made in duplicate and are accurate within 0.2 microgram.

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12. Davis, C. B., and Curtis, G. M.: Blood Iodine Studies: Quantitative Determination of Iodine Content of Blood, J. Lab. & Clin. Med. **18**:24, 1932.

A study of these results leads inevitably to the conclusion that the liver plays an important rôle in the metabolism of iodine. In practically all our cases of cholecystic disease of long standing as well as in the acute fulminating type the iodine content of the blood was abnormally high.

ALIMENTARY VARIATION IN IODINE CONTENT OF BLOOD

This aspect of the study of the iodine content does not seem to have received much attention from investigators. In 1933 Elmer and Luczynski [13] presented to the Biological Society of Lwów, Poland, a short note on the excretion of iodine in the bile in the fasting subject and within a short time after meals.

According to Elmer and Luczynski, certain authors (Y. Maruno) have maintained recently that in rabbits there is no physiologic incorporation of iodine in the bile. Nevertheless, many other investigators have found that physiologic iodine is present in rabbits' bile. But as the amounts found by these different workers vary greatly, it is evident that its presence in the bile must be very inconstant, ranging between wide limits, with the possibility of high values being reached under certain conditions. By contrast, in the blood there is always a relatively fixed amount of iodine, the highest figures never surpassing 20 micrograms per hundred cubic centimeters of blood. In the bile of rabbits have been found values varying from 15 to 62 micrograms per hundred cubic centimeters of blood (Maurer and Ducrue); in the bile of cattle, from 3.4 to 32.5 micrograms (Pfeifer), and in the bile of dogs, from 13 to 113 micrograms (Schittenheim and Eisler). The reason for such wide variations should be ascertained. It is noteworthy that not one of these investigators has mentioned whether the estimations were taken before or after meals.

With a view to establishing the normal ratio of the iodine in the bile to the other constituents of this body fluid for a twenty-four hour secretion period, the technic previously described was used in experiments on twelve rabbits. Bile was collected from nine rabbits during the fasting period (at least from twelve to fifteen hours after the last meal) and from three other rabbits immediately after eating (the ration consisted of beet roots, hay and oats). The values for the iodine content of bile obtained during fasting and that of bile examined immediately after the taking of food are widely different. This difference depends evidently on whether the bile is tested after fasting or after the ingestion of food. The values obtained after fasting have a rather narrow range (from 4 to 14 micrograms per hundred cubic centimeters

13. Elmer, A. W., and Luczynski, Z.: L'excrétion d'iode par la bile, à jeûne et après le repas, Compt. rend. Soc. de biol. **114**:1340, 1933.

of bile), being similar to those obtained for blood. The values for iodine obtained directly after eating are always higher (from 27 to 69 micrograms). Thus it is perfectly evident that the amount of physiologic iodine present in the bile at any given time will be greatly influenced by alimentation, which is diametrically opposed to the behavior of iodine in the blood. For example, in one instance bile examined three hours after eating gave values of 55 micrograms per hundred cubic centimeters of blood, but five hours later the values had fallen to 34 micrograms.

In regard to the twenty-four hour excretion of iodine in the bile, the studies of Elmer and Luczynski gave values of from 2.8 to 26 micrograms during fasting and of from 20.7 to 82.2 micrograms after eating.

There is strong evidence, therefore, that the marked variations in the values for the iodine content of bile, their sudden and violent upward fluctuations, as noted by the aforementioned investigators, are influenced not only by seasonal and age conditions but by the time (fasting or after feeding) when the specimens to be tested are secured.

Finally, it must be admitted that the liver plays an important rôle in the metabolism of iodine and that immediately after food enters the digestive tract the liver acts to eliminate the iodine constituents by way of the bile.

In conclusion, Elmer and Luczynski proved that the amount of iodine in the bile is sharply influenced by alimentation. During fasting the values remain within comparatively narrow limits (from 4 to 14 micrograms per hundred cubic centimeters of bile). On the other hand, after eating the values rise sharply (as high as 69 micrograms). Therefore, the liver plays an important and immediate rôle in the metabolism of iodine.

The part played by the liver in the metabolism of iodine continued to interest Elmer and Luczynski,[14] for somewhat more than a year later a second note on their observations was published. They continued to study the behavior of iodine simultaneously in both blood and bile, in the fasting state and after the taking of food. In experiments on five rabbits, the iodine in the blood was estimated after a twenty-four hour fast. The iodine in the bile after fasting was not measured, but was estimated on the basis of median values derived from previous experiments on nine rabbits. The figures for the iodine content of the bile after fasting did not range between very wide limits; their minimum was 9.2 micrograms per hundred cubic centimeters of bile, closely approximating those for the iodine content of the blood.

14. Elmer, A. W., and Luczynski, Z.: Rôle du foie dans la régulation du taux de l'iode dans le sang, Compt. rend. Soc. de biol. **115**:1717, 1934.

After examinations were made of the blood during fasting, the animals were given a twenty-four hour alimentation of beet root, oats and hay. The bile was collected ninety minutes after the last feeding. At the same time a sufficient quantity of blood was obtained. The figures obtained show that the iodine content of the blood did not rise to any great extent (from a minimum of 13.2 micrograms up to 16.4 micrograms per hundred cubic centimeters of blood), while the iodine in the bile, on the contrary, showed a marked rise after the taking of food (from 9.2 micrograms to 45 micrograms).

It is evident that alimentary iodine is eliminated into the digestive tube, principally by the liver through the bile. In following up the fate of this iodine in the digestive canal, one is impressed by the fact that iodine appears in but very minute quantities in the stools. The amount of iodine excreted in the stools of experimental animals, all of which were on the same diet, varied from 2 to 11 micrograms in the twenty-four hours. The amount excreted in the bile far exceeds this, as the figures for iodine in the bile ranged between 32 and 82 micrograms in twenty-four hours.

One is forced to the conclusion that this divergence between the excretion of iodine in the stools and its excretion in the bile can be explained only by resorption by the blood stream of the iodine originally excreted into the digestive tube with the bile. The iodine thus enters the portal vein and completes a continually repeated cycle: from the digestive canal to the portal vein, from the portal vein to bile, from bile to the digestive canal and so on ad infinitum.

One might theorize that during the first stage of this cycle, when the iodine enters the circulation after a meal, the liver does not permit the iodine to accumulate in the blood until it reaches a high value; and that in proportion as the alimentary hyperiodemia (excess of iodine in the blood) is lowered, the iodine is once more resorbed into the digestive canal. Without doubt, the liver plays the part of regulator of the proportion of iodine in the peripheral blood in that it forces throughout the entire circulation the maintenance within comparatively narrow limits of a nicely adjusted balance of iodine in the blood.[14]

CLINICAL CONFIRMATION

The findings of these Polish investigators have been closely duplicated in my own clinic. In making our determinations we have used the method described by Trevorrow and Fashena [15] in 1935. As already stated, our original object was to obtain diagnostic aid in determining the extent of the thyrotoxicosis in our patients with goiter. We were

15. Trevorrow, V., and Fashena, G. J.: Determination of Iodine in Biological Material, J. Biol. Chem. **110**:29, 1935.

sadly disillusioned after the idea had been put into practice for some time, because, although some patients suffering from hyperthyroidism did show an increase of iodine content of the blood, others—and the condition of some of them was as grave as that of any patients we have seen—gave values well within normal limits. This happened even when myxedema was in evidence. In our experience the results of the test for the iodine content of the blood in cases of goiter are sadly confusing when compared with the dependence we are able to place on the basal metabolism readings.

These findings have led us to the conclusion that iodine deficiency may not be the causative factor in the production of goiter, and the results obtained by others would seem to point in the same direction. The average ratio of inorganic to organic iodine in the cases in the clinic is 17 per cent. In reports from European clinics it averages 1 : 2. All our results emphasized the importance of the liver in the metabolism of iodine.

SUMMARY

The conclusion drawn from our studies and clinical applications was that determination of the iodine content of the blood might be a better test of hepatic function in cases of cholecystitis of long standing than the dye tests now in general use. This is because the liver is here working with a normal constituent of the blood, whereas when dyes are introduced artificially, as in the bromsulphthalein test, the introduction of a foreign element may well cause abnormal responses by the liver and disturb function appreciably. At present we are administering dextrose for several days before operation to all our patients with diseases of the gallbladder who have a high iodine content of the blood. This we believe to be far more effectual in preventing "liver deaths" than the administration of dextrose postoperatively. We have not yet been able to judge from the iodine content as to the most favorable time for performing operation, but are tentatively assuming that when it is below 100 micrograms per hundred cubic centimeters of blood one may operate with reasonable safety.

HEADACHE AFTER SPINAL ANESTHESIA

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Various explanations have been given for the postoperative headache which occasionally follows spinal anesthesia. Most of them can be classified under the headings of: (*a*) seepage of cerebrospinal fluid after spinal puncture,[1] (*b*) irritative meningitis [2] and (*c*) contamination of the material injected, causing irritation of nerve tissue.[3]

Recently considerable has been said regarding factors which render the anesthetic agent irritating to nerve tissue and thus produce postoperative headache.[3a] It has been claimed that contamination by antiseptic solutions used for sterilization of the skin (needle puncture through skin dripping with iodine) caused headache; also that hypertonicity resulting from dissolving crystals of procaine hydrochloride in cerebrospinal fluid was a potent factor in the production of headache. Further, it has been stated that the p_H of the solution is also important.

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1. (*a*) Peluse, S.: Post-Spinal-Anesthetic Headache, Illinois M. J. **67**:372, 1935. (*b*) Evans, C. H.: Possible Complications with Spinal Anesthesia: Their Recognition and Measures Employed to Prevent and to Combat Them, Am. J. Surg. **5**:581, 1928. (*c*) Nelson, M. O.: Postpuncture Headaches: A Clinical and Experimental Study of the Cause and Prevention, Arch. Dermat. & Syph. **21**: 615 (April) 1930. (*d*) Heldt, T. J.: Lumbar Puncture Headache, M. J. & Rec. **129**:136, 1929. (*e*) Weinstein, M., and McHugh, J. P.: One Thousand Cases of Spinal Anesthesia, ibid. **135**:507, 1932. (*f*) De Courcy, J. L.: New Methods of Controllable Spinal Anesthesia: The Use of Pitkin's Method in One Hundred Cases, Am. J. Surg. **5**:620, 1928. (*g*) Pitkin, G. P.: Spinal Anesthesia, in Lewis, Dean: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1935, vol. 1, chap. 5, pp. 22-23. (*h*) MacRobert, G.: The Cause of Lumbar Puncture Headache, J. A. M. A. **70**:1350 (May 11) 1918.

2. Stillwell, W. C.: Lumbar Anesthesia: Résumé of Seven Hundred and Fifty-One Cases, Minnesota Med. **15**:73, 1932. Anderson, E. R.: Complications of Spinal Anesthesia, Journal-Lancet **51**:73, 1932. Frazier, C. H.: Surgery of the Spine and Spinal Cord, New York, D. Appleton & Company, 1918. Parker, H. L.: Headache Following Diagnostic Spinal Puncture, Proc. Staff Meet., Mayo Clin. (supp. 1) **4**:369, 1929. Evans.[1b] Heldt.[1d] Pitkin.[1g]

3. (*a*) Harrison, P. W.: Postanesthetic Headache, Arch. Surg. **32**:99 (Jan.) 1936. (*b*) Babcock, W. W.: Spinal Anesthesia in Fact and Fancy, Surg., Gynec. & Obst. **59**:94, 1934. (*c*) Braun, H.: Localanesthesie, ed. 3, Leipzig, Johann Ambrosius Barth, 1914. Evans.[1b]

With a view to obtaining definite information regarding these assertions, we deliberately contaminated the solution made by dissolving procaine hydrochloride in cerebrospinal fluid by the addition of tincture of iodine and a solution of 2, 4, 6-trinitrophenol. We also compared the effects of using procaine hydrochloride dissolved in physiologic solution of sodium chloride, tap water and distilled water with procaine hydrochloride dissolved in cerebrospinal fluid.

METHOD

The experiment was conducted in five parts, twenty-five patients being used in each group. The anesthetic agent used was procaine hydrochloride, in doses

TABLE 1.—*Data on Postoperative Headache in Group 1 After Spinal Anesthesia*

Case	Date	Age	Operation	Headache
1	4/30	28	Appendectomy	None
2	5/10	25	Hernioplasty; appendectomy; resection of ovary	None
3	5/11	18	Appendectomy	None
4	5/12	37	Appendectomy; suspension of uterus	None
5	5/12	45	Appendectomy	None
6	5/14	55	Vaginal hysterectomy; perineorrhaphy	None
7	5/13	51	Excision of osteoma of foot	None
8	5/13	50	Amputation of cervix; interposition; Bell-Beattner operation; perineorrhaphy	None
9	5/13	27	Cholecystectomy; appendectomy	None
10	5/13	19	Appendectomy; oophorectomy on right	None
11	5/14	26	Open reduction for fractured patella	None
12	5/14	44	Hernioplasty	None
13	5/14	18	Appendectomy; resection of ovary	None
14	5/14	31	Hernioplasty	None
15	5/14	44	Cholecystectomy; appendectomy; suspension of uterus	None
16	5/14	37	Appendectomy	None
17	5/15	55	Bilateral hernioplasty	None
18	5/15	60	Exploratory operation for carcinoma of rectosigmoid region with metastasis to liver	Preoperative
19	5/16	34	Bilateral hernioplasty	None
20	5/16	33	Bilateral hernioplasty; hemorrhoidectomy	None
21	5/16	28	Bilateral hernioplasty	None
22	5/16	27	Left oophorectomy; appendectomy	None
23	5/16	21	Appendectomy	None
24	5/17	28	Excision of pilonidal cyst	None
25	5/17	32	Appendectomy	None

of 150 mg. All the injections were made between the second and the third lumbar vertebra with as nearly the same force and speed as possible, in an attempt to secure uniformity of introduction into the subarachnoid space. The injections were made with the Labat needles (22 gage), which we always use for this type of procedure.[4] No attempt was made to discriminate between types of headaches or degrees of severity. If any headache was felt, it was recorded.

Group 1.—To 150 mg. of procaine hydrochloride dissolved in 4 cc. of cerebrospinal fluid, 1 minim (0.062 cc.) of tincture of iodine was added, and the resultant mixture was injected into the subarachnoid space. The operation was performed, and headache was awaited. The results are recorded in table 1.

4. Koster, H.: Spinal Anesthesia (with Special Reference to Its Use in Surgery of the Head, Neck and Thorax), Am. J. Surg. **5**:554, 1928. Koster, H., and Kasman, L. P.: Spinal Anesthesia for the Head, Neck, and Thorax: Its Relation to Respiratory Paralysis, Surg., Gynec. & Obst. **49**:617, 1929.

The patient in case 18 on whom an exploratory operation was done for carcinoma of the rectosigmoid region, had a preoperative frontal headache for several days. At operation, miliary peritoneal and hepatic metastases were found. Postoperatively the patient continued to complain of frontal headache. Weeks subsequently there developed personality changes, an increase in intracranial pressure and ocular changes, all indicative of cerebral metastasis.

Group 2.—To 150 mg. of procaine hydrochloride dissolved in 4 cc. of cerebrospinal fluid, 1 minim of a solution of trinitrophenol (6 per cent trinitrophenol in 60 per cent alcohol) was added, and the resultant mixture was injected into the subarachnoid space. The operation was then performed, and headache was awaited. The results appear in table 2.

Two patients in this series complained of headache postoperatively.

TABLE 2.—*Data on Postoperative Headache in Group 2 After Spinal Anesthesia*

Case	Date	Age	Operation	Headache
1	5/18	29	Left salpingectomy; appendectomy	None
2	5/18	28	Hemorrhoidectomy	None
3	5/18	66	Interposition; perineorrhaphy	None
4	5/18	13	Appendectomy	None
5	5/18	40	Appendectomy; separation of pericholecystic adhesions	None
6	5/19	33	Cholecystectomy; sterilization; appendectomy	None
7	5/19	43	Supracervical hysterectomy; appendectomy	2 days
8	5/19	53	Choledochostomy; cholecystectomy; appendectomy	None
9	5/19	39	Supracervical hysterectomy; oophorectomy; appendectomy	None
10	5/19	32	Supracervical hysterectomy; left oophorectomy	None
11	5/19	43	Supracervical hysterectomy; oophorectomy	None
12	5/19	24	Herniоplasty; appendectomy	None
13	5/19	16	Appendectomy	None
14	5/19	51	Panhysterectomy; appendectomy	None
15	5/19	35	Cholecystectomy; appendectomy; sterilization	3 days
16	5/20	36	Appendectomy	None
17	5/20	44	Supracervical hysterectomy; oophorectomy; appendectomy	None
18	5/20	53	Hemorrhoidectomy	None
19	5/20	24	Appendectomy	None
20	5/20	24	Appendectomy; resection of ovary	None
21	5/21	11	Appendectomy	None
22	5/21	35	Cholecystectomy; appendectomy	None
23	5/23	39	Cholecystectomy; appendectomy	None
24	5/22	36	Herniоplasty	None
25	5/22	17	Appendectomy	None

Group 3.—One hundred and fifty milligrams of procaine hydrochloride was dissolved in 4 cc. of sterile physiologic solution of sodium chloride, and the resultant mixture was injected into the subarachnoid space after 4 cc. of cerebrospinal fluid was withdrawn. The results as regards postoperative headache are shown in table 3.

Only one patient in this group complained of headache postoperatively.

Group 4.—One hundred and fifty milligrams of procaine hydrochloride was dissolved in 4 cc. of sterile tap water, and the resultant mixture was injected subarachnoidally after 4 cc. of cerebrospinal fluid was withdrawn. The results as regards headache are shown in table 4.

Two patients in this group had headache postoperatively.

TABLE 3.—*Data on Postoperative Headache in Group 3 After Spinal Anesthesia*

Case	Date	Age	Operation	Headache
1	6/ 4	19	Appendectomy	None
2	6/ 4	47	Hernioplasty	None
3	6/ 5	35	Cholecystectomy; appendectomy	None
4	6/ 5	48	Supravaginal hysterectomy	1 day
5	6/ 8	42	Thyroidectomy	None
6	6/ 6	29	Cauterization of cervix; tracheloplasty	None
7	6/ 8	26	Closure of gastrocolic fistula	None
8	6/ 6	13	Appendectomy; resection of ovary	None
9	6/ 7	45	Supracervical hysterectomy; appendectomy	None
10	6/ 7	16½	Appendectomy	None
11	6/ 7	25	Appendectomy	None
12	6/ 8	53	Perineorrhaphy; Kelly's plication of urethra	None
13	6/ 8	18	Appendectomy	None
14	6/ 8	35	Perineorrhaphy; myomectomy; oophorectomy; appendectomy; hemorrhoidectomy	None
15	6/ 8	25	Appendectomy	None
16	6/ 9	33	Repair of anterior and posterior wall; supracervical hysterectomy	None
17	6/ 9	57	Appendectomy	None
18	6/10	21	Salpingectomy for ectopic pregnancy; appendectomy	None
19	6/10	57	Vaginal hysterectomy; perineorrhaphy	None
20	6/11	32	Left salgingo-oophorectomy; appendectomy; suspension of uterus	None
21	6/11	27	Cholecystectomy; appendectomy	None
22	6/11	20	Appendectomy	None
23	6/11	32	Supracervical hysterectomy; oophorectomy; appendectomy	None
24	6/11	32	Appendectomy	None
25	6/11	16	Appendectomy	None

TABLE 4.—*Data on Postoperative Headache in Group 4 After Spinal Anesthesia*

Case	Date	Age	Operation	Headache
1	5/26	58	Splenectomy	None
2	5/26	61	Gastrectomy; Murphy's button gastro-jejunostomy	None
3	5/26	29	Hernioplasty	None
4	5/26	36	Left oophorectomy	2 days
5	5/26	20	Bilateral hernioplasty	None
6	5/26	25	Myomectomy suspension; oophorectomy	2 days
7	5/26	43	Perineorrhaphy	None
8	5/27	46	Supracervical hysterectomy; appendectomy	None
9	5/26	11	Appendectomy	None
10	5/27	34	Supracervical hysterectomy; cholecystectomy; appendectomy; oophorectomy	None
11	5/26	42	Appendectomy	None
12	5/29	33	Hernioplasty; appendectomy	None
13	5/29	35	Hernioplasty; appendectomy	None
14	5/29	30	Bilateral oophorectomy; appendectomy	None
15	5/29	29	Appendectomy	None
16	5/29	41	Excision of pilonidal cyst	None
17	5/29	36	Hernioplasty (Gallie's)	None
18	5/30	59	Hernioplasty, incarcerated femoral	None
19	5/31	35	Bilateral oophorectomy; appendectomy	None
20	6/ 2	22	Hernioplasty, scrotal	None
21	6/ 2	62	Hernioplasty, scrotal	None
22	6/ 2	4½	Hernioplasty, inguinal	None
23	6/ 2	30	Appendectomy	None
24	6/ 3	30	Diagnostic curettage for carcinoma of uterus	None
25	6/ 3	47	Supracervical hysterectomy; oophorectomy; hemorrhoidectomy	None

Group 5.—One hundred and fifty milligrams of procaine hydrochloride was dissolved in 4 cc. of distilled water, and the resultant mixture was injected subarachnoidally after 4 cc. of cerebrospinal fluid was withdrawn. The results as regards postoperative headache are shown in table 5.

TABLE 5.—*Data on Postoperative Headache in Group 5 After Spinal Anesthesia*

Case	Date	Age	Operation	Headache
1	7/13	57	Separation of adhesions	None
2	7/13	50	Supracervical hysterectomy; appendectomy	None
3	7/13	25	Appendectomy; hemorrhoidectomy	None
4	7/13	37	Appendectomy	None
5	7/13	11	Appendectomy	None
6	7/13	24	Appendectomy	None
7	7/14	37	Appendectomy; sterilization; myomectomy	None
8	7/13	19	Appendectomy	None
9	7/14	47	Hernioplasty	None
10	7/14	66	Resection of sigmoid colon	None
11	7/15	60	Exploratory; biopsy	None
12	7/16	36	Exploratory; appendectomy	None
13	7/15	34	Supracervical hysterectomy; right oophorectomy; appendectomy	None
14	7/14	15	Appendectomy	None
15	7/15	21	Appendectomy; resection of ovary	None
16	7/16	65	Hernioplasty	None
17	7/16	40	Supracervical; hysterectomy; oophorectomy; appendectomy	None
18	7/15	19	Appendectomy	None
19	7/15	45	Appendectomy	None
20	7/15	54	Resection of intestine (ileitis)	None
21	7/16	21	Repair of hydrocele	None
22	7/16	26	Appendectomy	None
23	7/17	27	Appendectomy	None
24	7/17	54	Excision of varicosities	None
25	7/18	36	Appendectomy; myomectomy; sterilization; perineorrhaphy; biopsy of intestine	None

COMMENT

In an editorial by one of us [5] concerning the criteria of scientific proof, the point was made that uncontrolled biologic phenomena could not be used as significant data unless the material represented large values numerically. Thus it was shown that in our clinic, where spinal anesthesia was used as a routine for all major operations, as many as a hundred consecutive patients would frequently be anesthetized in this manner without a single instance of postoperative headache occurring, and then without any recognizable departure from the routine previously used, four or five subsequent patients would have headache. With one of these groups of one hundred headache-free patients as the criterion, it could have been said that the technic employed obviated the occurrence of postoperative headache. These next four or five patients would have

5. Koster, H.: Evaluation of the Results of Treatment, Am. J. Surg. **20**: 157, 1933.

demonstrated how erroneous the conclusion was. In a controlled series, however, in which individual factors are tested, comparatively small numbers can give significant results.

It seems hardly likely that contamination of injected fluid with iodine could produce postoperative headache. Iodine precipitates procaine hydrochloride, and this reaction is the basis for one of the chemical tests for procaine hydrochloride. Therefore, the iodine itself could not act as an irritant. If the insoluble compound formed by iodine and procaine hydrochloride is the irritating factor, then it must be very potent, since the amount of iodine which could be carried by the tip of the needle from dripping skin through approximately 3 inches (7 cm.) of tissues before the arachnoid is reached must be very small—certainly a minute fraction of a minim. The failure to produce headache uniformly in the twenty-five cases in which the solution of procaine hydrochloride was deliberately contaminated with 1 minim of tincture of iodine suggests strongly that contamination with iodine is not a potent factor in the development of postoperative headache after spinal anesthesia.

In our clinic, where spinal anesthesia has been induced in approximately 11,000 instances in the past eleven years, a solution of 6 per cent trinitrophenol in 60 per cent alcohol has been used for preparation of the skin. If contamination by solutions used for this preparation is responsible for headache, then in our cases it must have been either the trinitrophenol or the alcohol which was the contaminant. However, the failure to produce headache uniformly in the twenty-five cases in which one minim of solution of trinitrophenol was deliberately added to the anesthetic agent injected again suggests strongly that it is not a causal agent.

The relation of hypertonicity to the development of postoperative headache has never been demonstrated. The experiments with saline solution and water as solvents for procaine hydrochloride have failed to yield any significant information, and it must be conceded that from the data it cannot be concluded that postoperative headache depends on the hypertonicity or the hypotonicity of the injected solution.

No reliable data concerning the effect of varying the p_H on the development of postoperative headache are available. The p_H [6] of cerebrospinal fluid plus procaine hydrochloride is 7; that of tap water and procaine hydrochloride is 5.93, and that of distilled water plus procaine hydrochloride is 5.63. After the injection of procaine hydrochloride dissolved in distilled water, headache was not uniformly produced. However, that is not surprising when it is remembered that only 4 cc. of the procaine hydrochloride solution is injected into a fluid the minimum amount of which is at least 50 cc. and which contains

6. The p_H determinations were made with a glass electrode.

considerable buffer substance. As a matter of fact, if three minutes after the injection of 4 cc. of distilled water containing 150 mg. of procaine hydrochloride into the subarachnoid space a sample of cerebrospinal fluid is withdrawn, it is found to have a p_H of 7.

It can be seen from the tables that if the one patient in group 1 who had a headache preoperatively is left out of the consideration, there were five patients with postoperative headache among the one hundred who were used in the experiments. The ordinary incidence of postoperative headache in our experience is 5 per cent.

The experiments were carried out on the first four groups of patients consecutively. There was an interval between the experiments on group 4 and group 5, during which time one hundred and thirty-five persons were anesthetized with procaine hydrochloride dissolved in cerebrospinal fluid. Of this number, not a single person had headaches postoperatively.

CONCLUSIONS

1. The addition of either tincture of iodine or a solution of trinitrophenol to procaine hydrochloride dissolved in cerebrospinal fluid does not add to the risk of development of headache postoperatively.

2. Hypotonicity or hypertonicity as occasioned by using tap water, saline solution or distilled water also is not a factor in the production of headache postoperatively.

3. Buffer substances are present in cerebrospinal fluid in sufficient quantities to render innocuous ordinary solutions used to develop anesthesia which might have a p_H as low as 5.63.

INTESTINAL OBSTRUCTION

AN ATTEMPT AT AN IMPROVED DISCUSSION OF ITS PATHOLOGIC PHYSIOLOGY AND TREATMENT BASED ON A SIMPLE CLASSIFICATION AND ON PAST EXPERIMENTAL AND CLINICAL EXPERIENCE

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In 1933, in conjunction with Dr. B. F. Stout, I initiated some experiments on intestinal obstruction. Since that time continued experimental and clinical work on this problem have contributed toward a conception of this disease which is more comprehensive and proper than the conception we previously held.

We have been encouraged by others to believe that certain phases of our previous work, which will be discussed briefly later in this paper, may have been of some value in clarifying somewhat one fundamental aspect of the condition.[1] I venture to present here a simplified classification of intestinal obstruction which I feel is amenable to a comprehensive, yet brief and improved, discussion of its known pathologic physiology. The majority of the points mentioned have been previously reviewed by others. Certain aspects of the classification and discussion, however, have not.

It must be admitted that a perfect classification of any disease is impossible as long as there are unsolved aspects of it, and certainly there is more to be learned about obstruction. The importance of an impaired blood supply in cases of obstruction has not been as widely appreciated as it should have been because of the confusion attending the many theories and discussions which have been carried on over the world regarding unknown aspects of obstruction. In accepting the importance of the impaired blood supply as I do in the following discussion, I do so on the basis of the work of Kader, Murphy and Vincent, Gatch, Gatch and Culbertson, McIver, Wilkie and many others. The importance of this factor has been proved beyond question. It must be acknowledged that investigators do not know the exact mechanism of the deleterious action of an impaired blood supply. It

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1. Donaldson, J. K., and Stout, B. F.: Mesenteric Thrombosis: Arterial and Venous Types as Separate Clinical Entities, Am. J. Surg. **29**:208 (Aug.) 1935.

may, furthermore, be acknowledged that there may be some legitimate dispute as to the primary importance of neurogenic and other factors in distention associated with obstruction. From a practical standpoint, however, one is justified in accepting any hypothesis as a working basis as long as this hypothesis procures end-results which are as good as, or superior to, any other end-results. The following trend of thought will at present procure these results.

In accepting the theory that distention may produce sufficient ischemia of the mucous membrane of the intestine to cause a lethal absorption of toxin, one accepts dogma which has good support. Gatch and Culbertson [2] are the latest workers to offer evidence in this direction. It probably would be unfair to say that other influences never play a part in distention. It seems probable, however, that when distention is

Classification of Intestinal Obstruction *

I Direct Obstruction of the Lumen		II Indirect Obstruction of the Lumen	
1. With primary interference with blood supply	2. Without primary interference with blood supply	1. With primary interference with blood supply	2. Without primary interference with blood supply
a (a) Folded strangulated loop in cavity	a (c) Simple high or low obstruction with no folded loop	a (e) Occlusion of mesenteric arteries without direct obtion of lumen	a (g) Postoperative ileus
b (b) Strangulated loop isolated from cavity, as in incarcerated hernia	b (d) High or low obstruction with added obstruction of folded loop	b (f) Occulsion of mesenteric veins without direct obstruction of lumen	b (h) Ileus from acute infectious disease or from other causes without direct obstruction of lumen

* It is to be acknowledged, of course, that for academic completeness subclassifications dealing with the wide variety of specific causes of obstruction should be added to this classification. These details of subclassification, however, should not be confused with the fundamentals of pathologic physiology with which the classification given here deals.

the cause of death, as it sometimes is, it is always sufficiently marked to interfere with the blood supply to the mucous membrane, even though other factors may possibly enter into the picture. As far as present day knowledge is concerned, however, the proper treatment is the same whether or not one chooses to accept the factor of an impaired blood supply in distention as one of the main factors in the morbid picture.

THE TWO CHIEF CONCERNS IN OBSTRUCTION

Before referring to the classification in the table, I am assuming, then, with the possible reservations mentioned previously, that in practically all cases of obstruction there are two main problems. 1. The first one is the potential loss of fluid and salts. The seriousness of this factor is widely appreciated and needs no further consideration for the moment. 2. The second is potential interference with the blood supply to the

2. Gatch, W., and Culbertson, C. G.: Circulatory Disturbances Caused by Intestinal Obstruction, Ann. Surg. **102**:619 (Oct.) 1935.

intestine, either by primary interference or by interference secondary to distention. The physiologic relationship of other factors to these two highly important ones will be discussed later.

The classification of intestinal obstruction appears in the accompanying table.

It may be noted that all types of obstruction are divided into two large classes: (I) that in which there is an actual direct blockage of the lumen of the intestine, such as may rise, for example, from an adhesion or from an intra-intestinal or extra-intestinal foreign body or tumor, and (II) that in which the lumen of the intestine is indirectly obstructed but not closed, as in postoperative ileus. These two main divisions are further divided into two groups on the basis of one of the two chief concerns in obstruction, namely, the blood supply: (1) that group in which the blood supply is primarily interfered with and (2) that in which the blood supply is not primarily interfered with but in which it may be secondarily threatened by distention. On the simple foundation of these parts of the classification, one can rapidly build an understanding of diagnostic and therapeutic considerations. Before proceeding, however, with further discussion of the relation of secondary factors a brief consideration of certain differences caused by strangulation of the arterial supply as against an uncomplicated strangulation of the venous return from the intestine should be given.

NECESSITY FOR APPRECIATING THE DIFFERENCE BETWEEN ARTERIAL AND VENOUS MESENTERIC OCCLUSION

The differences between pure venous mesenteric occlusion and arterial mesenteric occlusion have a bearing on the fundamental physiology of obstruction as a whole. Previous to 1934 or 1935 it seemed to have been generally accepted that the end-results of occlusion of the mesenteric veins and those of occlusion of the mesenteric arteries were the same. Mention had been made of the anatomic difference of the two types, but a full realization of the pathologic differences between the two had never, as far as I know, been appreciated previous to the work of Dr. Stout and myself on this subject.[3] The opinions expressed in our published reports have been confirmed or at least upheld by others since that time. Ochsner has referred to clinical cases of purely venous thrombosis of the mesenteric vessels in which recovery occurred without resection. Certain parts of the work done by Knight and Slome[4] evidently gave results similar to ours.

3. Donaldson, J. K., and Stout, B. F.: Mechanics of Absorption in Intestinal Obstruction, Texas State J. Med. **30**:455 (Nov.) 1934. Donaldson and Stout.[1]

4. Knight, G. C., and Slome, D.: Intestinal Strangulation, Brit. J. Surg. **23**:821, 1936.

Held and Goldbloom [5] reported a case of venous thrombosis of the mesenteric vessels following repeated administration of phenolphthalein. So it seems an established fact that there are vast pathologic and clinical differences between pure venous occlusion of the mesenteric vessels and pure arterial occlusion, provided the lumen of the intestine remains sufficiently unobstructed in the former. Occlusion of some of the mesenteric veins does not always cause secondary arterial thrombosis; it does not necessarily cause gangrene of intestinal tissue if the intestinal lumen remains sufficiently patent to empty the involved loop of collecting fluids, and it does not per se cause paralytic ileus; it does give rise to a different clinical picture than that produced by arterial occlusion. Failure to realize these facts has been responsible for some misinterpretation of the problem of obstruction. For example, statements of good surgeons have depreciated to a certain extent the danger of gangrenous intestine, cases being cited in which, after resection of a loop of blackened intestine which had evidently been present for days, the patient recovered. Likewise, it has been said that the omentum and the peritoneum will often wall off a gangrenous loop of intestine in the peritoneal cavity, thereby decreasing the danger. The latter mechanism and result may take place in a case of incarcerated hernia, but the tremendous fulminating danger of gangrene should never be minimized. Unquestionably confusion of the loops of blackened but not gangrenous intestine which occur in cases of venous occlusion with truly gangrenous loops in cases of arterial occlusion has been responsible for some misunderstanding. I have often seen experimentally a blackened intestinal loop in a case of purely venous occlusion which "walled off," with resulting clinical recovery, but I have never seen true gangrene of the intestine in an animal or in man go through a similar process to successful recovery. Such an incident, if it occurs at all, must be extremely rare.

MECHANISM OF THE SECONDARY FACTORS

The mechanism of the secondary factors of intestinal obstruction, as outlined in the table, are discussed briefly.

a (*c*). In the simple type of obstruction in which no direct interference with the blood supply is present, what is the mechanism of the developing pathologic process? If the obstruction is high it is generally known that vomiting with loss of fluid and salts rapidly supervenes and may be the most important part of the picture. Distention may not develop, because the unobstructed intestine may automatically regurgitate through the pylorus. Consequently, interference with the

5. Held, I. W., and Goldbloom, A. A.: Three Rare Intra-Abdominal Cases, S. Clin. North America **14**:389 (April) 1934.

blood supply may not occur.[6] In this type of obstruction infusions of saline solution, combined with decompression by the use of the Wangensteen or nasal catheter if distention is present, will give immediate temporary relief. Obstruction has righted itself after such treatment. Temporization carries, however, the responsibility of assuming surety as to type of obstruction.

If the simple obstruction is lower in the small bowel, serious vomiting will develop later. Distention of the intestine will appear, eventually interfering with the blood supply to the mucous membrane. Distention will be harder to control by decompression through the nasal catheter because of the loops of intestine folding on themselves.

If the simple obstruction is in the large bowel, vomiting will become a serious factor only late in the disease, if ever. Distention in the large bowel may not cause the production or absorption of toxin directly but may cause a rupture of an ischemic area in the cecum, even before serious subjective symptoms have presented.[7]

b (*d*). If the obstruction is of the looped type in which the bowel is folded on itself, obstructing a segment as well as the main continuity of the intestine, there is immediately superimposed on the consideration as to the level of obstruction the added factor of the obstructed loop. This loop may rapidly become distended, bringing ischemia to its mucous membrane or additional constriction to its primary blood supply. Temporization procedures in this type are extremely dangerous.

a (*a*). If one has a gangrenous loop of intestine free in the peritoneal cavity anywhere, its level is of secondary consequence. Unless the area of gangrene is removed promptly from the cavity, death will follow. With a folded loop, however, in which there is interference with the blood supply, one should realize the different pathologic pictures which may be produced by purely venous occlusion as against arterial occlusion. As previously stated, every blackened intestinal loop is not gangrenous. Also, there is a difference between the advancing pathologic condition in a folded loop to which the venous apparatus and and the lumen are both occluded and that of an intestine in which the veins supplying it are closed with the intestine not occluded. In the former the collection of fluid and distention of the intestine are rapid, with

6. Jenkins, H. P., and Beswick, W. F.: Prolongation of Life for Seventy Days in High Intestinal Obstruction by Administration of Sodium Chloride and Nutritive Material Below the Site of Occlusion, Arch. Surg. **26**:407 (March) 1933.

7. Saeltzer, D. V., and Rhodes, G. K.: Diastasic Perforation of the Normal Cecum, Ann. Surg. **101**:1257 (May) 1935.

tremendous bacterial proliferation and interference with the arterial supply soon presenting.

b (*b*). If a strangulated loop is isolated within an incarcerated hernia so tightly that no absorption through the mesentery or peritoneal cavity can occur, it is for the moment, to an extent, a simple obstruction. In operating for this type of obstruction one should be extremely careful when gangrenous intestine is freed from the incarceration to prevent its toxic content from moving into the lumen of the intestine remaining in the peritoneal cavity, if the latter bowel is damaged at all by distention. Otherwise a severe dose of toxin may be absorbed.

a (*e*). In obstruction occurring from paralysis secondary to arterial mesenteric occlusion in which no direct obstruction of the lumen is present, one is, as with gangrenous intestine of other types, concerned only with immediate operation.

b (*f*). If the occlusion of the vessels is purely of the venous type without obstruction of the lumen, the clinical course which has been described by Dr. Stout and myself [1] may possibly end in recovery if the involvement of the intestine is not too extensive. Prompt surgical intervention, however, is probably, as a rule, the treatment of choice.

a (*g*) and *b* (*h*). In the last two groups, in which a primary paralytic ileus is present, as for example in acute infectious diseases or in the primarily paralytic postoperative type, abdominal exploration is not indicated. Other decompression measures may be life saving.

The differential diagnosis of the foregoing types of obstruction will not be discussed here. There are points of difference between all types. It can readily be seen how complicated the differential picture between many of them usually would be, however, if the diagnosis were to be made early and with surety. Furthermore, general statistics reveal that operation for simple obstruction within twenty-four hours after the onset produces a low mortality. The mortality is still lower if operation is done earlier. For the gangrenous types, as previously stated, the most prompt surgical intervention possible is essential. Absorption of toxin probably starts within thirty minutes after the blood supply is strangulated.[4] If operation is delayed more than twelve hours after the onset of gangrene, a very high death rate is to be expected. I know of no mortality statistics which subdivide the twelve hour period in reference to gangrene, but I feel that with every single hour's delay after gangrene supervenes the mortality is increased.

So when one keeps in mind the different pathologic pictures of obstruction, the difficulty of an early clinical differentiation between most of them and the mortality statistics as related to early operation in most types of the disease, it is easy to understand the grave

responsibility one assumes when one uses temporization measures to postpone operation in all but the primary paralytic types, as listed in *a* (*g*) and *a* (*h*) or sometimes in *b* (*f*) of the classification. Fortunately, these types are fairly easily differentiated from the others.

SUMMARY

A discussion of the pathologic physiology and treatment of intestinal obstruction as based on a simple classification is presented. The majority of the points in this discussion have been previously mentioned, but certain aspects of it are offered as an improvement over some conceptions formerly held.

Previous experimental and clinical work citing differences in the pathologic picture of the arterial and of venous types of mesenteric occlusion are discussed. These differences as they are related to certain fundamentals of the problem of obstruction as a whole should be more fully appreciated.

A REVIEW OF UROLOGIC SURGERY

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KIDNEY

Anomalies.—Shih and Char [1] stated that congenital solitary kidney may be defined as an anomalous condition in which one kidney is absent because of a disturbance of growth of the nephrogenic tissue in embryonic life and the existing kidney has developed from one renal bud. If the solitary kidney is healthy, congenital absence of the opposite kidney does not give rise to pathognomonic symptoms, and the condition may exist for years without the patient being aware of it.

It cannot be overemphasized that recognition of solitary kidney is of paramount importance and should merit the great concern of the urologic surgeon. A congenital solitary kidney is compatible with normal physiologic function, and a patient with this anomaly maintains full working capacity. The condition is of clinical significance only in the presence of renal disease.

Operation should be recommended only when it is absolutely imperative, and surgical procedures should be as conservative as possible. Experience has demonstrated that the risk of operation on the solitary kidney varies directly with the impairment of function and the degree

1. Shih, H. E., and Char, G. Y.: Congenital Solitary Kidney, Chinese M. J. **50**:821-826 (June) 1936.

of infection and that delay in operating on a solitary kidney until urinary obstruction or anuria has developed definitely increases the operative mortality. In the presence of good renal function and in the absence of infection, a great variety of surgical procedures have been and may be performed on the solitary kidney, with gratifying results.

This anomaly is of interest from the standpoint of its genesis and of importance because of its significance to the patient. This condition, even though it is infrequent, should be kept in mind by all those who are interested in surgical treatment of renal conditions.

Char, Shih and Wen [2] reported 14 cases of duplication of the kidney and ureter. The pathologic picture, symptomatology, diagnosis, prognosis and treatment were considered. The authors pointed out that the complicating pathologic lesion may be found in either the ectopic or the normal segment of the kidney, in spite of the general belief that the upper ectopic segment is usually the seat of disease. From clinical and embryologic studies, it is concluded that as long as proper connections exist between the supernumerary kidney and its ureter it is capable of the functions of a normal organ. Their findings tend to endorse the view that these anomalies develop as a result of a separate outbudding from the mesonephric duct or as a bifurcation of the original ureteral bud.

Mayers [3] stated that congenital displacement is to be distinguished from acquired displacement of the kidney. Marked displacement of congenital origin is uncommon. One of the rarest types is a condition in which both kidneys are on the same side of the body. There is a similarity between various forms of displacements and anomalies of structure which often causes confusion in the terminology; for example, a horseshoe kidney which is situated entirely on one side of the midline is identical with a fused type of crossed renal ectopia.

The embryologic factors involved were considered. There are two chief schools of thought: (1) that which believes displacement is due to failure of ascent of the kidney and (2) that which believes that it is attributable to descent of the kidney. Both schools believe that the mechanism involved is closely related to the process of vascularization and that other related factors are variations in the location and branching of the ureteral bud. The marked forms of displacement occur early in embryonic life.

The fused type of crossed renal ectopia is perhaps ten times more frequent than the unfused type. A search of the literature revealed reports of 19 cases which were in all probability true cases, or cases of

2. Char, G. Y.; Shih, H. E., and Wen, I. C.: Duplication of the Kidney and Ureter, J. Urol. **36**:305-326 (Oct.) 1936.

3. Mayers, M. M.: Crossed Renal Ectopia, J. Urol. **36**:111-122 (Aug.) 1936.

the unfused type, of crossed renal ectopia. Undoubtedly many other cases which have been reported in the literature as of the fused type may be of the unfused type. Mayers reported 7 such cases.

Nineteen cases of crossed renal ectopia, not including the 7 reported by Mayers, presented the following characteristics: In 8, the patients were women, and in 10, men; in 1 case the sex was not reported. The right kidney was involved in 3 cases, the left in 15 cases and both in 1 case. The crossed kidney was under the uncrossed kidney in 17 cases and over the uncrossed kidney in 1 case. In 1 case both kidneys were crossed.

Mayers added to those reported in the literature 1 case in which the condition bore all the characteristics of an unfused type of crossed renal ectopia. The patient was a man whose right kidney was uncrossed and whose left kidney was crossed over and placed under the right. There was pyelitis of both kidneys, and the right kidney contained three large calculi. Diagnosis was made by examination and confirmed at operation. This case is unique as calculi were present in the uncrossed partner of the combination. As far as Mayers could determine, there is no other case reported in the literature in which this situation exists.

Lower [4] described a case of fused kidney in which three almost distinct kidneys had fused into one mass; two of these were in essentially normal position and were joined together by a third kidney lying medially and horizontally in front of the spinal column. This third kidney had a complete pelvis and a ureter, which anastomosed with the ureter of the left kidney at about its middle third. This median supernumerary kidney, which thus constituted the isthmus of a horseshoe kidney fused at the top, was removed with its anomalous ureter, leaving the patient with a right and a left kidney, both of which were functioning well, as was revealed by a postoperative intravenous urogram.

The author, who has had a series of 23 cases of fused kidney, pointed out that extreme care must be taken in establishing the diagnosis in such cases, because the symptoms are so largely referable to the gastro-intestinal tract as to be misleading. Many erroneous diagnoses of acute or chronic appendicitis, gallstones, duodenal ulcer, chronic ulcerative colitis and tumor of the colon have been made by practitioners who did not think of the possibility of horseshoe kidney and hence did not employ urography and the complete laboratory facilities to clear up the diagnosis.

The cardinal symptoms of horseshoe kidney, as summed up by Gutierrez, are umbilical or epigastric pain, extending to the lumbar

4. Lower, W. E.: The Problem of the Fused Kidney, J. Urol. **35**:588-595 (June) 1936.

region, chronic constipation and perhaps other gastro-intestinal disorders, and urinary disturbances associated with early signs of nephritis. These symptoms are attributable to the pressure exerted by the horseshoe kidney lying across the spine and close to the great abdominal vessels, the solar plexus and the abdominal sympathetic and parasympathetic nerves.

A complete history should be taken with special reference to subjective as well as to objective symptoms. A tumor situated in the midline may be palpable and is often tender, and pain produced on bending backward sometimes will suggest the presence of a horseshoe kidney. Laboratory studies of the blood and urine should be made. A roentgenographic examination is essential, and this may give the first indication that a horseshoe kidney is present. The important points in establishing a diagnosis from roentgenograms are the outline and position of the kidney, the possible delineation of the isthmus, abnormalities in the shape and contour of the pelvis and calices (the lowermost calices usually point inward toward the midline), the abnormal position of the ureters, which in the horseshoe kidney usually enter the lateral and not the internal aspect of the renal organ, and, finally, any shortening of the ureters, stricture or kinking. The diagnosis is made easier if the kidney contains stones, since if multiple wedge-shaped calculi are present the direction of the axis of the kidney can often be determined from the way the stones are placed.

When symptoms are so severe that the patient seeks aid, an indwelling catheter should be inserted at once to secure drainage and to relieve infection; rest in bed, administration of urinary antiseptics and cathartics and intravenous injection of physiologic solution of sodium chloride should also be employed. Permanent cure can be obtained, however, only by surgical intervention, consisting of division of the isthmus with or without nephropexy, according to the degree of motility of the kidneys.

Ptosis.—Gouverneur and Cachin[5] stated that most of the poor results from operations on movable kidneys in the past have been caused by a failure to recognize the correct indications. The mere presence of a movable kidney, with pain, was enough to invite operation, without any inquiry about the morphologic condition of the pelvis, ureter and kidney or the amount of infection in the urinary tract. The authors insisted on the paramount importance of taking retrograde ureteropyelograms with the patient in the vertical position and of taking into consideration the site of the pain, which shows the true position of the kidney, the form of the pelvis and, especially, the topography of kinks of the ureter.

5. Gouverneur, R., and Cachin, Charles: Le traitement chirurgical des ptoses rénales: Indications; technique; résultats, J. de chir. **47**:754-770 (May) 1936.

They have operated on 28 patients with movable kidney associated with marked functional troubles. The results, both anatomic and functional, were always excellent. In all but 5 cases retrograde ureteropyelograms were taken, the intravenous method of urography being used. It requires more delicate judgment to recognize the indications for operation than to perform the operation, for the technic is very simple. The patient should be studied for some time before the operation, as there is no need for hurry; several examinations should always be made. One should not operate on a patient with several other operative scars, for renal ptosis may be only the most apparent element of some general disease. Mild pyelonephritis in a ptotic kidney is an indication for operation; when a long course of treatment does not result in improvement, operation is indicated, and if the condition is a frank pyelonephritis, this is all the more true. Pyuria, which is not too excessive, is another indication for operation. If hydronephrosis is present, one must make sure that this is secondary to the ptosis and not a congenital condition, for in the latter case reposition will do no good.

At operation, the authors advocated high reposition. Despite some opinions to the contrary, their films revealed good results from this method. The old technics of Guyon and Albarran are inadequate, and yet they are the ones most frequently used. The incision used by Gouverneur and Cachin is slightly different from the usual lumbotomy; it is shorter, commences a little above and internal to the anterosuperior iliac spine and goes obliquely toward the costolumbar angle; two finger-breadths below this it becomes vertical and continues directly upward to the tenth rib. It is only during the course of the operation that the situation of the kidney can be learned exactly, for it depends on the morphologic relations of the ribs, the thorax and the bed of the kidney. In effecting fixation, the linen threads are drawn from below upward and from within outward through the diaphragm, the two leaflets of the diaphragmatic pleura and the intercostal pleura and the intercostal muscles. A fault to avoid is that of passing the threads which have gone through the intercostal space and the diaphragm outward from the kidney bed; this can easily happen and will result in allowing the kidney to come only partially upward; the left hand placed under the cupola must serve as a guide to the needle. The sutures are tied two and two, the anterior together and the posterior similarly; the assistant in the meantime pushes the kidney into its bed and supports the lower pole. A small suspensory hammock is made for the lower pole of the perirenal fat and the lower part of the renal fascia and is tied above the twelfth rib or sometimes even above the eleventh rib. The patient should be kept in bed for three weeks, after which a course of exercises should be prescribed to strengthen the abdominal muscles.

Smith, McKim and Rush [6] reported their findings after a study of 238 nephropexies performed on 204 patients in the fourteen years prior to 1934.

They stated that there are four factors in ptosis of the kidney that may be of importance in the production of symptoms: 1. Tension on, and torsion of, the renal pedicle usually causes a sensation of heaviness and weight in the side affected and frequently interferes with the return flow of blood through the renal vein to such an extent as to produce attacks of renal colic in patients in whom there may be no evidence of renal stasis.

2. The excessive stimulation of the sympathetic nerves as a result of the constant pull on the splanchnic area may manifest itself in many ways and probably plays a rather important rôle in the production of the symptoms of the dyspepsia so frequently found in these cases. The frequency of intense headaches and of pain that is referred to a point midway between the scapulae also may result from this excessive stimulation. The so-called "neurasthenia" so commonly found in cases of neglected ptosis of the kidney is undoubtedly caused by excessive stimulation of the sympathetic nerves.

3. The sagging of the midportion of the duodenum can be demonstrated easily by fluoroscopic examination of the gastro-intestinal tract, particularly if this is made with the patient standing and in conjunction with retrograde pyelography.

4. The frequency with which ureteral kinks are demonstrated in cases of ptosis of the kidney is probably quite misleading. It is felt that these kinks are not of any particular clinical importance unless there is evidence of renal stasis or of chronic infection of the renal pelvis.

Two types of altered renal mobility are recognized: the asymptomatic and the symptomatic. The latter type comprised at least 60 per cent of all the authors' cases. They have chosen as a basis for discussion a classification of the latter group based entirely on symptomatology, although the extent of alteration in mobility in each of these groups is rather constant.

The cases are classed in four groups: Those in group 1 are characterized by attacks of acute excruciating pain, simulating renal colic, and the other symptoms of renal ptosis are seldom present. This type of pain is found almost as frequently on the left as on the right side. Often the patient can date the onset of his symptoms from the time of some unusual physical exertion or an accident. The cases in group 2 are characterized by marked gastro-intestinal symptoms suggesting pyloric

6. Smith, P. G.; McKim, G. F., and Rush, T. W.: Nephropexy for Disabilities Due to Abnormal Renal Mobility, Ann. Surg. **103**:924-934 (June) 1936.

or duodenal obstruction. Occasionally these are so severe that they have been the cause of a previous operation, such as appendectomy or cholecystectomy. Those in group 3 are characterized by occasional attacks of rather severe renal colic and a marked tendency toward a recurrent pyelitis and hematuria. Symptoms of chronic dyspepsia are usually present. There is in these cases a definite tendency toward neurasthenia. Examination reveals the kidney to have a movement of from 1½ to 3 inches (3.57 to 7.6 cm.) and frequently gives evidence of urinary stasis. It is in this group, which comprised 48 per cent of their series, that the authors had the most uniformly satisfactory results. The cases in group 4 are characterized by more or less constant heaviness and dragging in the side, and usually symptoms suggestive of chronic renal infection are present. If these symptoms are on the right side, symptoms of mild, chronic dyspepsia are usually present also. Examination reveals a very low-lying kidney and usually a dilated and infected renal pelvis.

The vast majority of unsatisfactory postoperative results are attributable to one or more of the following causes: (1) failure to restore the kidney to its proper position, (2) production of excessive trauma about the renal pedicle or the ureter at the time of operation and (3) failure to recognize coexistent pathologic changes in the kidney or adjacent organs.

Calculi.—Marion [7] stated that after the successful removal of renal, pyelic or ureteral stones the general condition of the upper portion of the urinary tract in some cases is disappointing, as the patient frequently continues to suffer from urinary disturbances. In some cases an existent infection continues, or the kidney performs its excretory duties poorly; pockets may exist which have become cicatrized, and in the course of a few years pyonephrosis supervenes. Another tendency of kidneys that have been calculous is toward sclerosis. The kidney atrophies and becomes deformed, and the calices and pelves take on atypical characters, notwithstanding the fact that no fresh calculi have formed.

In some cases in which a ureteral calculus has been removed in the expectation that the patient would be relieved of urinary troubles, relief has failed to materialize, and, instead, the ureter has become cicatrized and its canal totally obliterated. This obliteration progresses silently and results in considerable atrophy of the kidney on the same side. Several cases were cited to illustrate these various pathologic changes. In some cases in which it might have been possible to reconstruct a working ureter, the function of the kidney continued to be deficient. In

7. Marion, G.: De l'évolution des reins après l'ablation des calculs du rein, du bassinet où de l'uretère, J. d'urol. **42**:193-204 (Sept.) 1936.

other cases so much periureteritis was present that the continuity of the ureter could not be restored, and the patient must carry a urinary fistula all his life because of changes in the ureter and the kidney.

From all these cases Marion concluded that the prognosis in operations for suppression of reno-ureteral calculi must be reserved, since without reappearance of calculi lesions may be established as the result of sclerosis, which finally lead to destruction of an organ which it had been hoped could be saved by removing the cause of the primary infection.

[COMPILERS' NOTE.—It should be borne in mind that the removal of calculi from the upper portion of the urinary tract is only the beginning of the necessary treatment. It is essential after removal of the stones to institute measures to secure good drainage and to relieve the infection. These two desiderata can be readily obtained by nephrostomy followed by routine cystoscopic treatments with dilations of the ureters and lavage of the renal pelvis. These treatments should be carried out at first once a week, then once in two or three weeks and later once a month; it may even be necessary to repeat them once or twice a year for a long period. Finally, the urologic condition of the patient should be checked occasionally for a reasonable length of time by intravenous urograms, and sometimes a special dietary regimen also should be instituted.

When such control is not properly maintained, we must agree with Marion that the outcome of surgical intervention for relief of nephroureterolithiasis is very poor, particularly in clinic cases in which the condition is beyond control. But when the fundamental principles of drainage, relief of infection and administration of a proper diet are carried out under the systematic control of a follow-up clinic, the results are gratifying.]

Priestley and Osterberg[8] briefly discussed the current theories of the etiologic factor of renal calculi, namely, stasis, infection, vitamin deficiency, other dietetic errors, metabolic disorders, endocrine disturbances, abnormalities of the p_H of the urine, various alterations of the urinary colloid-crystalloid relationship, local ulcerating lesions in the collecting portion of the kidney, etc. It seems unlikely that the etiologic factor is the same in all types of calculi. For example, cystine, urate and phosphate stones are obviously formed by a different process.

The authors studied 193 cases in which stones composed chiefly of calcium oxalate, of calcium phosphate associated with varying amounts of calcium carbonate or of urates were removed from the urinary tract. In each case the chemical composition of the stone was determined,

8. Priestley, J. T., and Osterberg, A. E.: The Relationship Between the Chemical Composition of Renal Calculi and Associated Bacteria, J. Urol. **36**:447-459 (Oct.) 1936.

and in many cases the preoperative p_H of the urine was determined and cultures of the urine and calculi were made. Cystine, xanthine and other uncommon types of stones were not included in the study because the data on these calculi seemed insufficient to be significant. There were 93 oxalate stones, 71 phosphate stones and 29 urate stones.

It was noted that calculi of different chemical composition are not found with equal frequency in all parts of the urinary tract. For example, 82.8 per cent of the oxalate stones were removed from the kidney or ureter, and, in contrast, only 48.3 per cent of urate stones were removed from the upper part of the urinary tract. Approximately 62 per cent of the phosphate calculi were removed from the kidney or ureter, and the remainder were removed from the bladder. Apparently urate and phosphate stones form somewhat more frequently in the bladder than do oxalate calculi. It seems possible that the site of origin of a calculus may be of etiologic significance. It was found that approximately 25 per cent of the phosphate and urate stones were bilateral, whereas only 13 per cent of the oxalate stones were bilateral. The average incidence of bilateral calculi in cases of nephrolithiasis is approximately 15 per cent. Recurrent stones are more often composed of phosphates than of oxalates. The rapidly reforming stone is almost invariably of phosphatic origin, although the original calculus may have been of a different nature. In this regard it is mentioned that phosphates normally occur in the urine in much larger amounts than do urates or oxalates.

All types of renal calculi may be associated with infection; however, in some cases infection is apparently present prior to precipitation of the stones, and in other instances it is a secondary development. Phosphate stones were found associated with bacteria in the urine in approximately 59 per cent of cases, whereas oxalate stones were found in infected urine in only 28 per cent and urate stones in 21 per cent of cases. Cultures of the stones themselves usually correspond closely to the cultures of the urine, although this is not always true. Many different types of bacteria are found associated with calculi, Escherichia coli being found most frequently. The relatively high incidence of Proteus ammoniae in association with phosphate stones is emphasized. Multiple types of bacteria were found more often in the presence of phosphate stones than they were with any other type of calculus. The wide variety of organisms that may be present indicates that under proper circumstances many different types of bacteria may be associated with the precipitation of stone.

The importance of p_H of the urine in the etiology of lithiasis was considered. Although the exact chemical sequelae of variations in p_H are not clearly understood, the resultant changes in solubility, colloidal

protection against precipitation of crystalline material, ionic equilibrium and other factors may have an important influence on the formation of stones. The p_H of the urine was invariably higher when infection was present. Normally, phosphate stones are associated with the highest p_H, oxalate stones with a somewhat lower p_H and urate stones with the lowest p_H of all.

Barney and Mintz [9] stated that although hyperparathyroidism is responsible for between 4 and 5 per cent of all cases of urinary stone, in almost 70 per cent of the cases of this disease stones may be present. It is also true that in about 38 per cent of cases of hyperparathyroidism patients may have pathologic changes in both the bones and the urinary tract. This disease does not seem to be a factor in the production of bilateral urinary lithiasis. The symptoms and signs of urinary lithiasis in cases of tumor of the parathyroid glands do not differ from those attributable to other causes. After removal of the tumor stones do not recur. Barney and Mintz expressed the belief that today no physical examination is complete without a careful study of the calcium and phosphorus content of the blood, especially if urinary lithiasis is present or is suspected.

Higgins [10] stated that diet is of definite benefit to the following groups of patients and that the best results are secured among such patients:

In the first group are the patients in whom there is a tendency to the recurrent formation of calculi after operation. A review of the cases at the Cleveland Clinic up to 1932 revealed recurrence in 16.4 per cent, but since a special diet has been prescribed as a routine after operation, this has been reduced to 4.7 per cent. Higgins stated that it may be too early to report these figures, for two years is the maximal period since operation, but he definitely expressed the opinion that a dietary regimen should be included in the postoperative care in addition to the therapeutic procedures employed previously. By following this principle, the cause and not the effect alone of the disease is treated.

In the second group of patients are those who have passed stones at frequent intervals but in whom larger calculi cannot be demonstrated in the kidney. At the Cleveland Clinic 40 of the patients in this group have been free from symptoms for two years.

The third group consists of orthopedic patients in whom stones develop while they are in the hospital. As a general rule, the stones are

9. Barney, J. D., and Mintz, E. R.: The Relation of the Parathyroid Glands to Urinary Lithiasis, J. Urol. **36**:159-167 (Aug.) 1936.

10. Higgins, C. C.: Urinary Lithiasis: Experimental Production and Solution with Clinical Application and End-Results, J. Urol. **36**:168-177 (Aug.) 1936.

composed of calcium and magnesium phosphate, namely, stones which form in an alkaline urine. If the high vitamin A acid ash diet is prescribed for these patients while they are forced to remain in a recumbent position, thus shifting the reaction of the urine to the acid side, the chemical possibility of the development of such calculi is reduced to a minimum.

Higgins seemed to be quite certain that if the patients who live in those communities in the United States which have been reported as stone areas could receive adequate amounts of vitamin A, the formation of calculi could be prevented in a large percentage.

It is difficult to say when stones will undergo dissolution. In one case a stone had not changed in size for eleven months until an attack of colic occurred recently. The stone was situated in the lower calix of the kidney, and some days after the attack of colic a considerable amount of sand was passed, and the large stone disappeared. On the other hand, in many cases response is not secured; the reason for this is not known. In an effort to explain this, Higgins is studying the outer coating of the stones and making a more careful quantitative analysis of them. After operation the renal pelvis is lavaged with 1 per cent solution of phosphoric acid, as suggested by Randall.

Higgins has studied a series of more than 35 cases in which complete urologic examination revealed renal calculi. These stones have been caused to undergo complete dissolution and have disappeared after the patient had followed the prescribed dietetic regimen.

In view of the fact that patients who have a duodenal ulcer and who are treated by the Sippy routine are given considerable amounts of alkali and as a general rule have a strongly alkaline reaction of the urine, Higgins expressed the belief that cod liver oil or halibut liver oil should be prescribed as a routine. He emphasized this because many cases have been reported in which calculi developed or were passed while the patients were being treated by this method.

Higgins,[11] in discussing prevention of recurrent renal calculi, stated that recurrent calculus formation occurs with sufficient frequency to be a seriously complicating factor in the surgical treatment of nephrolithiasis. Empirical treatment which has been employed in the past does not reduce the percentage of recurrence below 10 or 15. The alkaline or acid ash diet with a high vitamin A content should be prescribed after operation, the constituents of which depend on the p_H of the urine and the chemical constituents of the calculus. A group of 31 patients who previously had had frequent attacks of renal colic and had expelled

11. Higgins, C. C.: Prevention of Recurrent Renal Calculi, Surg., Gynec. & Obst. **63**:23-34 (July) 1936.

small stones spontaneously have been free from symptoms for more than two years on dietary management. During the past four years, since this diet has been used in conjunction with other therapeutic agents, renal calculi have recurred in 4.7 per cent of the cases studied. This percentage, which is higher than was anticipated, was believed to be attributable to the fact that roentgen examination was not performed as a routine after operation and, thus, that some of the recurrences may have been false in type.

Hydronephrosis.—Campbell [12] reported a case of hydronephrotic renal destruction secondary to a ball-valve papilloma at the pelvic outlet. Chief interest focuses on the diagnosis; attention is directed to the urographic filling defect caused by the growth but which might justifiably be thought to be produced by a nonradiopaque calculus. Nephrectomy is the usual treatment.

Ormond [13] reported 6 unsuccessful operations for hydronephrosis, 5 of which were for obstruction at the ureteropelvic juncture. Of the latter, 2 were converted into apparent successes by second operations. Experiences such as these do not warrant dogmatic or authoritative statements. Ormond stated that in view of this experience and in view of the results reported in the literature he was justified in drawing the following tentative conclusions:

The Heineke-Mikulicz type of operation should be distrusted in the future. It seems to be best suited to cases in the early stage in which there is no infection, and in many such cases reimplantation of the ureter has given satisfactory results. Ureteropyeloplasty has no advantages over reimplantation. It is rather difficult to perform with precision, for the kidney and the ureter are drawn up out of their natural positions in order to obtain exposure, and the line of incision and repair might be distorted when the organs are restored to their normal positions.

Resection of the ureteropelvic juncture should be favored, and the ureter should be cut on a slight bias to lessen the likelihood of stricture from contraction of the suture line and reimplanted into the lowest portion of the pelvis, with accurate apposition of the cut edges. The ureter should not be allowed to protrude into the pelvis at all. This is not difficult, and with a catheter running through the cortex and pelvis of the kidney and down the ureter, the first sutures nearly always can be made as the ureter and pelvis lie in situ. In every case a splinting catheter should be used, there being no haste about removal. In the

12. Campbell, M. F.: Hydronephrosis Due to Ball-Valve Obstruction by Papilloma at Ureteropelvic Junction, Am. J. Surg. **33**:291-293 (Aug.) 1936.

13. Ormond, J. K.: Unsuccessful Plastic Operations for Hydronephrosis, J. Urol. **36**:512-528 (Nov.) 1936.

presence of acute, or marked, infection, preliminary nephrostomy should be performed. In every case in which the kidney is not bound down by adhesions, preventing mobility, nephropexy should be performed.

Plastic operation should be reserved for those cases in which conservation of renal function is imperative or for those cases in which the desirability of conservation of renal function outweighs the chance of increased expense, danger and loss of time.

Campbell [14] stated that vascular compression of the ureter is not uncommon in children. Vessels which produce the obstruction are congenitally anomalous. Hydronephrosis is the important uropathy, and infection usually is present. The commonest symptoms are pain in the renal region, pyuria, hematuria, a mass in the loin and, after the advent of infection, fever. Most children with vascular obstruction of the ureter are treated for months for chronic pyelitis. In the absence of infection, the renal changes, as interpreted by urinalysis, are regularly diagnosed as those of chronic interstitial nephritis. Yet the correct diagnosis usually can be made preoperatively by a complete urologic examination. The correct diagnosis is often suggested by the excretory urogram. Delayed diagnosis and radical surgical treatment are usually reciprocal. Nonoperative treatment has no place. Conservative surgical treatment may be expected to save a gratifying number of injured kidneys. Unfortunately the medical profession is as yet insufficiently alert to the high incidence and importance of urologic disease in children. Because of the consequent delay in making the diagnosis, nephrectomy will necessarily be the treatment for fully half of the children with vascular ureteral blockage.

Renal Abscess.—Emmett and Priestley [15] reported a case of solitary renal abscess. The original roentgenogram of the urinary tract revealed a large shadow of a soft tissue mass in the left side of the abdomen. The shadow of the psoas muscle on the left side was much less distinct than that on the right. An intravenous urogram revealed a normal right kidney. The pelvis of the left kidney, which was approximately normal in size, was flattened on its lateral aspect by a soft tissue mass situated in the region of the lower pole of the kidney. The calices were elongated and distorted. The upper calix was flaring at its tip, and the middle calix was flattened against the pelvis. The lower calix was only partially visualized, and obliteration of its lower part was suggested.

At operation the upper half of the kidney appeared to be normal, but in the lower pole there was a large inflammatory mass which was

14. Campbell, M. F.: Vascular Obstruction of the Ureter in Children, J. Urol. **36**:366-387 (Oct.) 1936.

15. Emmett, J. L., and Priestley, J. T.: Solitary Renal Abscess (Carbuncle): Report of Case, Proc. Staff Meet., Mayo Clin. **11**:764-767 (Nov. 25) 1936.

densely adherent to the peritoneum and adjacent structures. During mobilization of the lower pole, some nonodorous pus was encountered. Nephrectomy was performed. The tissues, including the peritoneum, which had surrounded the lower pole, were indurated, inflamed and thickened. This region was packed with iodoform gauze, and the wound was closed loosely with a few interrupted sutures. In the lower pole of the kidney there was a large, well circumscribed abscess, with multiple points of discharge typical of the so-called renal carbuncle.

In contrast to the majority of renal lesions, the correct preoperative diagnosis of renal carbuncle is usually difficult to make, primarily because no characteristic deformity is revealed in the urogram. If the lesion is small, the outline of the pelvis and calices may be perfectly normal; if it is large enough to produce deformity, this deformity frequently simulates that of a neoplasm or cyst. In the roentgenogram diminution in intensity or absence of the shadow of the psoas muscle on the affected side, associated with scoliosis of the spinal column, may call attention to the condition, especially if considerable perinephritis is present.

Carbuncle of the kidney, like a smaller unilocular cortical abscess, is considered a manifestation of a blood-borne infection. It usually develops slowly over a period of some weeks or months, during which interval there is a paucity of symptoms. Depending on the duration and extent of the process, perirenal involvement will be slight or extensive. Treatment is surgical and consists of either resection of the carbuncle or nephrectomy. Removal of the kidney is usually advisable if the other kidney is normal, as conservative procedures are often followed by prolonged convalescence and nephrectomy may be necessary in the end.

Tuberculosis.—Mazzarelli [16] carried out experiments consisting of the inoculation of tubercle bacilli into the perihilar tissue of the kidney and into the wall of the ureter, by which he was able to produce tuberculosis of the renal pelvis and the corresponding renal parenchyma.

In the majority of the experiments inoculation was followed by generalized tuberculosis, which included also a renal localization. The tubercle bacilli evidently came to the kidney by way of the blood stream. In some cases, however, the tuberculous changes were strictly confined to the zone of inoculation, that is, to the corresponding kidney and the regional lymph glands, without any localization in other organs; in these instances diffusion to the kidney by way of the blood stream must be excluded, and diffusion by the lymphatics must be assumed. These cases were relatively rare, but they prove that this mode of infec-

16. Mazzarelli, M.: Considerazioni e ricerche sulla patogenesi della tuberculosi renale, Arch. ital. di urol. **13**:119-166 (March) 1936.

tion of the kidney is a possibility. Infection by this route has been admitted in cases of pulmonary localization, and there is no reason why it should not be possible for other organs as well. All authors agree that tuberculosis of the kidney is practically always secondary, although Albarran collected from the literature reports of 6 cases of primary renal tuberculosis. After an extensive review of the literature, Mazzarelli pointed out that ascending infection was once believed to be the common route for renal tuberculosis, Albarran himself being among those who held this view. Today, however, it is believed that this is the route only under favorable conditions, such as exist when the sphincter of the ureteral meatus is weak or absent, so that vesicorenal reflux occurs.

The deep and superficial lymphatics of the kidney and also those of the fatty capsule empty into the corresponding para-aortic lymph nodes, which thus become the regional lymph nodes of the kidney. But these may also receive lymph from other abdominal and pelvic organs, such as the hilus of the kidney, the ureter, bladder, urethra, prostate gland, seminal vesicles and testes; all of these lymphatics were traced by the author. Between all of these lymph channels there are anastomoses, and any of them may flow into the same abdomino-aortic ganglions. In the lymphatic infection of the kidney three routes were distinguished: (1) the ascending ureteral route, (2) the retrograde route and (3) the route from nearby organs. Experiments were done to discover whether renal tuberculosis could be produced by the lymphatic route, through infection of the ureteral walls or the tissues about the pelvis or hilus, whether an inflammation of the testis could be started by the lymphatic route and, finally, the modes by which this infection is developed. The author found that he could produce specific changes which often remained localized at the point of inoculation or in nearby zones but were sometimes diffused. Thus, after one hundred and eighty days he found tuberculosis localized exclusively to the kidney or ureter in 4 of 25 experiments, which gives a relatively high percentage. In the other experiments there was most often a generalized tuberculosis, with concomitant renal lesions, which had developed because of injection by the hematogenous route, and therefore these were not counted. Apparently the bacilli are diffused along the submucous spaces, where there is a rich lymphatic network, and in cases of lymphatic infection they are carried upward by the lymphatic current to the renal pelvis.

Sutherland and Braasch [17] reviewed the development of the roentgen ray and its use in urologic diagnosis. Important anatomic character-

17. Sutherland, C. G., and Braasch, W. F.: The Value of Roentgen Rays in the Diagnosis of Renal Tuberculosis, Tubercle **17**:309-317 (April) 1936.

istics of the kidney were emphasized in their relation to the roentgenographic diagnosis of tuberculosis. The pathologic changes caused by early tuberculosis in the kidney were considered. A review was made of 1,314 cases in which the patients were treated surgically and the presence of renal tuberculosis was proved by microscopic examination. In 1,157 of these cases a preliminary plain roentgenogram of the genito-urinary tract was made, and in 237 cases (20.6 per cent) the findings were positive; that is, some abnormality was present which suggested the presence of a lesion in the genito-urinary tract. These abnormal findings included alteration in the size and contour of the soft tissue shadow of the kidney; more or less extensive calcification in the region of the kidney, which was occasionally misinterpreted as evidence of renal calculi; indeterminate types of shadow, and calcified lymph nodes. In the roentgenogram the margin of a tuberculous calcified area is usually rough and irregular, whereas that of a calculus tends to be more discrete and smooth in outline. Shadows of tuberculous calcifications are found more frequently in the region of the cortex, whereas those of calculi are commonly seen in the pelvis or in the calices. There is frequently a difference in the intensity of the shadow cast by a tuberculous lesion in contrast to that cast by a renal calculus. As mentioned previously, there was some evidence of abnormality in the plain roentgenogram in approximately a fifth of all cases. Retrograde and excretory urography were then employed in order to establish a definite diagnosis. At times excretory urography alone gives sufficient information on which to base diagnosis and treatment. Frequently, however, cystoscopy and retrograde pyelography are essential.

It is the consensus that renal tuberculosis is never a primary condition. In this series roentgenographic examination of the thorax was made in 911 cases. In 280 cases (30.7 per cent) there was evidence of pulmonary tuberculosis, which in the majority of cases was latent. In 83 of 1,314 cases tuberculous lesions were coexistent in bone. Fortunately, at present patients consult the physician earlier than they did formerly. Today renal tuberculosis is suspected when dysuria persists over a period of one or two months; the urine is stained for tubercle bacilli, and in cases in which the diagnosis is doubtful guinea-pigs are inoculated, cystoscopic examinations are made, the kidneys are catheterized and pyelograms are made. Renal tuberculosis in the advanced stage with severe ulceration and deformity of the bladder is encountered less commonly. It is generally believed that the condition is hematogenous and begins in the kidney rather than in the bladder. The infecting agent passes through the capillary system of the glomeruli and settles in some portion of the collecting system. Then, by a retrograde process, it

passes up the lymphatic structures and infects the cortex. The lesion is probably unilateral in the beginning and may remain so for a remarkably long time. The incidence of primary bilateral renal tuberculosis, on the other hand, is probably greater than was previously supposed; the possibility of spontaneous recovery in the early miliary type of renal tuberculosis must be recognized. The importance of preoperative and postoperative hygienic treatment in assuring the best prognosis cannot be overemphasized.

Definite limitations and possibilities of error in the use of the excretory urogram as a single method of diagnosis in cases of renal tuberculosis are mentioned. In the differential diagnosis the changes resulting from pyogenic pyelonephritis are most frequently confused with those of tuberculosis. In the urogram deformity occurring with pyelonephritis tends to be more commonly uniform; all of the calices are likely to be involved by inflammatory dilatation, and evidence of cortical involvement is much less frequent. In the retrograde urogram artefacts from overdistention or incomplete distention may simulate tuberculosis, and extravasation may cause shadows in the parenchyma distal to the tips of the minor calices which may be confused with those of cortical necrosis as a result of tuberculosis. Likewise, nephrolithiasis, when associated with pyelonephritis or pyonephrosis and cortical abscesses, may simulate tuberculosis closely in its urographic manifestations. Tuberculosis may invade the perinephric tissues, and the outstanding roentgenographic evidence will be obliteration of the shadow of the psoas muscle on the affected side. Carcinoma of the kidney not infrequently is attended by calcification in the primary tumor, and such calcification may be mistaken for tuberculosis. Likewise, necrosis may be caused by malignant involvement. Roentgenography does not play an important part in the identification of tuberculosis in the genital organs.

Weber [18] found that in nearly all instances the end of the ureter which had been sewed into the skin after nephrectomy for tuberculosis contained tubercle bacilli on culture on the second and third postoperative days. He considered this as a proof that the stump of the ureter is often the source of a fistula. In his cases the formation of a fistula postoperatively was much rarer when the ureter was cut after the renal pedicle was clamped and then tied and brought out to the skin. He recommended this as a standard procedure in nephrectomy for tuberculosis.

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18. Weber, Herbert: Zur Vermeidung postoperativer Fisteln bei Nierentuberkulose (Tuberkelbacillenkulturen aus dem Ureterstumpf), Ztschr. f. urol. Chir. u. Gynäk. **42**:416-428 (Dec.) 1936.

Pelz [19] stated that the microscopic examination of a stained smear of the urinary sediment in cases of renal tuberculosis often gave negative results. Results of inoculation of guinea-pigs are usually positive, but the method necessitates waiting too long. The culture method of Löwenstein gave positive results in 88 per cent of cases of renal tuberculosis and in 55 per cent of the cases of tuberculous epididymitis. Fifty-five patients were examined. It is interesting to note that sometimes cultures of blood were positive for tuberculosis at an earlier time than the cultures of the urine.

Hemorrhagic Cysts.—Barney [20] reported 2 cases of hemorrhagic cyst of the kidney. The hemorrhage in case 1 was acute and gave rise to a train of obscure subjective and objective symptoms. The etiology was unknown, but the possibility of infection or trauma and perhaps embolism or thrombosis should be considered. The presence of another cyst in the same kidney, which was thin walled and filled with serous fluid, increased the probability that what ended as a hemorrhagic cyst might well have started as a serous cyst.

In case 2 nothing was known of the antecedents of the condition. The fact that the kidney opposite to the one which contained the hemorrhagic cyst contained three serous cysts might allow one to follow the same train of thought as in case 1. On the other hand, the calcified wall surrounding the blood clot would indicate an ancient process, with symptoms so insignificant that the patient did not notice them.

In case 1 there were no symptoms, subjective or objective, previous to the onset of the hemorrhage. At this time the symptoms were very suggestive of renal colic, caused perhaps by calculus. There was in addition a strong suggestion of a rather severe but obscure hemorrhage. The pain and tenderness can be accounted for by the sudden increase of tension within the cavity of the cyst.

In case 2 there were evidently no signs or symptoms during life which could be elicited by the history or physical examination. The calcified wall of the cyst is indicative of a long-standing process, and the hemorrhage into it was not extensive enough to have caused symptoms at the time it occurred.

These 2 cases illustrate that cysts of the kidney may, and in fact often do, exist for an indefinite and probably a long time without giving rise to symptoms. The factors which bring about their recognition are pressure, pain, the presence of a tumor, intracystic pressure and acute hemorrhage.

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19. Pelz, S.: Nachweis der Tuberkelbazillen bei Urogenitalerkrankungen durch das Kulturverfahren nach Professor Löwenstein, Wien. med. Wchnschr. **86**:1027-1029 (Sept. 5) 1936.

20. Barney, J. D.: Hemorrhagic Cyst of the Kidney, J. Urol. **36**:602-608 (Dec.) 1936.

Hydatid Disease.—Begg [21] stated that a total of approximately 800 cases of hydatid disease of the kidney is available for study. The incidence of the disease fluctuates in a given country with the number of sheep, the living conditions, the level of culture and the efficacy of preventive measures.

Renal cysts may be classed according to their relation to the renal pelvis as open, closed and pseudoclosed. In the first type both the pericystic and the endocystic cavity communicate with the pelvis; in the second type neither cavity communicates with the pelvis, and in the third type, only the pericystic cavity, the ectocyst remaining unruptured. Symptoms are characteristic for each type of cyst. In the open cyst they consist of renal colic and the passage of hydatid elements in the urine; in the closed cyst the symptoms are usually attributable to pressure; in the pseudoclosed cyst the typical manifestations are intermittent attacks of pain localized to the loin due to colicky pain of the calix and perhaps urinary symptoms, such as hematuria or frequency, but no hydatid material is passed.

The etiology of hydatid disease of the kidney is that of hydatid disease in general. The industry of sheep raising, on the one hand, and insanitary conditions of life, on the other, contribute chiefly to its incidence and spread.

Unlike the liver, the kidney is almost invariably the site of one primary cyst only. In the larger series of cases the incidence of involvement of each kidney is equal, and bilateral cysts are rare. Nicaise found involvement of the right kidney in 197 cases, of the left kidney in 185 cases and of both kidneys in 12 cases. The sexes are equally vulnerable. Most patients are infected in childhood, and the third to the fifth decade is the commonest period for the development of symptoms. In the reported cases the youngest patient operated on was a child aged 2 years. The commonest site of the cyst is the cortex of the anterior surface at the upper and lower poles.

In the kidney, as elsewhere, the hydatid cyst develops slowly, though growth may be stimulated by trauma or pregnancy. Expansion is centrifugal, but the center point of the sphere is not static. As a rule the line of least resistance is followed, but in an effort to preserve its circular contour the cyst may burrow into the spleen, into the liver or into the tail of the pancreas. The hydatid may die of old age or lack of nutriment. There is a ring of large blood vessels in the pericyst, a striking feature microscopically. Thus ample serum is brought to the hyaline laminated membrane, from which the parasite can select its food supplies. Calcification hinders the osmotic process. The animal

21. Begg, R. C.: Hydatid Disease of the Kidney, Brit. J. Surg. **24**:18-40 (July) 1936.

feels the urge for more defensive propagation. Daughter cysts are born in large numbers and even granddaughter cysts. Tension may become low, and growth may be in abeyance or spasmodic. The whole tribe may perish and be buried in lime, or sepsis may supervene. Low grade life may, however, be maintained, even though the pericyst is heavily calcified.

The expanding pericyst may become incorporated in the stomach, spleen, pancreas, colon, liver, duodenum or vena cava. The adrenal glands may become inseparably fused. Such a welding of tissues becomes a danger at operation, chiefly if the surgeon confuses it with an ordinary adhesion and attempts to separate the inseparable. There is no reason why a large cyst at the upper pole should not rupture into the bronchial system. Complications within the urinary tract include hydronephrosis, pyonephrosis, lowering of capacity of the kidney on both sides from difficulty in micturition or chronic retention from an accumulation of membrane in the bladder, with or without bilateral ascending pyelonephritis. All are rare and usually are attributable to sepsis. The ureter on the affected side may become completely occluded.

Calculus associated with hydatid cyst is rare, even in such countries as Dalmatia, in which both conditions are common.

Symptoms may not appear for many years, and the patient may be ignorant of the existence of the cyst till the day of his death. A closed cyst may be found accidentally in a person who is perfectly well. The parasite may produce unexplained anaphylactic phenomena, such as urticaria or symptoms of obscure pressure. A closed cyst that grows toward the abdomen causes indigestion, pain and fulness after meals by encroaching on the stomach, or diarrhea, constipation or even complete obstruction by pressure on the colon.

In the case of an open cyst diagnosis is made from examination of the material passed. If this is only hydatid sand or brood capsules, the condition may be considered as merely caused by the passage of gravel, and the patient may have to wait some time before a microscopic examination of the sediment discloses hooklets and scolices. A calcified cyst may produce solid débris, which when passed is mistaken for calculus. A pseudoclosed cyst is demonstrated by a typical pyelogram. A closed cyst is most difficult to demonstrate. Clinically, it appears as a tumor of the hypochondrium or as a free and mobile tumor of the abdominal cavity. If the muscles are rigid, such a tumor may be missed during an attack of renal colic. The commonest error in diagnosing a tumor in the hypochondrium is to mistake a cyst on the left side for an enlarged spleen, especially in communities in which malaria is endemic, or one on the right side for a cyst of the liver. In the case of the former the special serum tests, with roentgen examina-

tion and pyelograms, usually clear up the diagnosis; in the case of the latter, serum tests are useless. A cyst at the upper pole of the kidney may produce a high area of dulness at the base of the lung of the corresponding side and has to be distinguished from an intrathoracic condition or a splenic cyst as well as from hydronephrosis. The greatest calamity in such cases is a diagnostic puncture. When there are no physical signs, routine urologic examination may reveal deformity of the renal pelvis, and the serum tests may eliminate other confusing renal conditions.

Roentgenographic examination may reveal a density due to the high saline content of hydatid fluid or a typical curvilinear shadow of a calcified pericyst. In all types of cases complete urologic investigation usually gives fairly conclusive information.

The precipitin test is rarely used. The complement fixation test, worked out by several persons, is a laboratory procedure requiring rigid conditions of technic to give its best results. The intradermal reaction of Casoni, taking into account both the immediate and the delayed reaction, is simple, practical and of great value.

From the statistics available, hydatid disease of the kidney appears on the whole to be relatively innocuous. Of the 474 cases of Nicaise, 20 per cent were found in the course of routine postmortem examination; 215 of the patients received no surgical treatment, and only 16 died as the direct or indirect result of the cyst. The first attack of colic and the passage of membrane may be the last in spite of an active parasite. Impairment of renal function to a dangerous level is rare even in cases of long standing, and the general health of the patient is seldom affected. Spontaneous cure occurs in many cases, though symptomatic cure is probably more common than anatomic.

Treatment is mainly surgical or expectant. Turpentine has been used to assist elimination of the daughter cysts. No intravenous therapy is effective. Nephrectomy was introduced by Bockel in 1887 to replace the universal method of marsupialization. Intervention must be governed by two considerations: In the first place the disease is benign, and a cyst once communicating with the pelvis as a rule ceases to grow because the level of tension required in the fluid for this purpose reopens the safety-valve. In the second place radical operation is difficult because of the dense adhesions and is not to be undertaken lightly.

As a rule operation is not indicated in the following circumstances: 1. After a first attack in which cysts are passed in the urine when investigation reveals that only a small cyst is present and that renal function is good on both sides. The danger of complications is small, and subsequent intervention may be undertaken if disabling symptoms or septic complications occur. 2. If the other kidney is absent, infantile

or functioning badly from any cause and no serious disability is caused by the hydatid. In the best hands any difficult operation on a kidney may lead to damage demanding nephrectomy, and the risk of operation is greater than that of the parasite. 3. If the cyst is calcified and dead, unless passage of the calcified fragments threatens damage to the urinary tract or is seriously disabling.

In most other cases nephrectomy, if possible, is the operation of choice if the other kidney is normal in function, for the following reasons: 1. The mortality is low, convalescence is short and health is quickly restored. 2. Secondary cysts may exist in the calix, making recurrence inevitable if the kidney is left. These cannot be detected during any conservative operation. 3. An apparently closed cyst may really be of the pseudoclosed type, and with conservative operations there is danger not only of recurrence but of infecting the urinary tract. 4. In many cases the whole of the pericyst cannot be removed, and in these instances recurrence is common. If the kidney is left, the old symptoms of renal colic and the passage of membrane will recur. When the kidney is removed, the recurring cyst will cause no trouble and in the course of many years will reach the surface in the loin, where it can be easily dealt with.

Circulation.—Anson, Richardson and Minear [22] studied the variations in the number and arrangement of the renal vessels of 400 kidneys. In only 35 per cent of 200 consecutively examined cadavers were the renal arteries of both sides arranged in the simplest pattern, namely, with a single vessel supplying each kidney. In 65 per cent of the 200 cadavers a unilateral or a bilateral anomaly of the renal arteries was present, a condition so regularly prevailing that it certainly should no longer be regarded as anomalous. In 20 per cent of the bodies the simple arrangement of renal vessels occurred on the right side, accompanied by supernumerary arteries on the left side; in 17 per cent, a single vessel supplied the left kidney and multiple vessels the right; in 28 per cent, multiple vessels supplied the right kidney, and in 28 per cent, multiple vessels supplied both kidneys. Of the 400 kidneys, 53 per cent were found to have a so-called normal arterial supply. The remaining 47 per cent possessed extra-arterial branches.

The authors encountered no kidney in which the number of supernumerary vessels exceeded four (three from the aorta to the hilus and one from the renal artery to the extremity). From the data obtained

22. Anson, B. J.; Richardson, G. A., and Minear, W. L.: Variations in the Number and Arrangement of the Renal Vessels: A Study of the Blood Supply of Four Hundred Kidneys, J. Urol. **36**:211-219 (Sept.) 1936.

on the renal tributaries of the inferior vena cava in the same group of 400 kidneys, it is strikingly evident that venous variations are relatively few.

Hyman [23] made a study of 6 cases of suppurative disease of the kidney complicated in 5 instances by suppurative thrombophlebitis of the renal vein; the diagnosis was confirmed by operation or postmortem examination. Since this condition is nearly always secondary to a suppurative lesion in the kidney, the diagnostic criteria are not sufficiently clearcut to differentiate thrombophlebitis from the primary disease of the kidney, which in 5 cases was a cortical abscess. The clinical picture is essentially one of sepsis with or without bacteremia. If sepsis is not controlled after adequate drainage of a suppurative focus in the kidney or after nephrectomy, thrombophlebitis of the renal vein should be suspected. It should be realized that the kidneys are often the seat of localized metastatic abscesses following cutaneous staphylococcic infections. With this type of infection, invasion of the blood stream by staphylococci not infrequently occurs. If after drainage operation and decapsulation of the kidney, the sepsis persists, nephrectomy should be done and the renal vein ligated as close to the vena cava as possible. If the sepsis persists after a primary nephrectomy, the renal vein should be suspected and explored.

Operation disclosed in 2 instances that thrombophlebitis may be present without causing any recognizable gross changes in the vein. This study further disclosed that in 3 instances the thrombotic process at the time of nephrectomy had already extended into the vena cava. One can well realize that under such conditions nephrectomy even with wide ligation of the renal vein might prove futile.

These 5 cases indicate definitely that suppurative lesions of the kidney act as a source of invasion of the blood stream by the production of a secondary thrombophlebitis. The mortality from this condition is unusually high, because in most instances the sepsis is already widespread before the nature of the disease is recognized.

Pain Syndromes.—Keyser [24] has previously advanced the proposition that pain in the upper part of the urinary tract occurs not infrequently when a small, if any, lesion can be demonstrated clinically and that after repeated scrupulous examinations from many points of view other than urologic, one is at a loss to understand the fundamental pathologic process involved. He presented the hypothesis, and some evidence substantiating it from a series of 60 cases, that nodal spasm of neurogenic

23. Hyman, Abraham: Acute Suppurative Thrombophlebitis of the Renal Vein, J. Urol. **36**:196-210 (Sept.) 1936.

24. Keyser, L. D.: Pain Syndromes in the Upper Urinary Tract: Their Mechanisms and Clinical Management, South. M. J. **29**:953-963 (Oct.) 1936.

background can simulate ureteral stricture and that the clinical course of most of his patients warranted the belief that spasm rather than organic stricture was most often the pain-producing mechanism.

He stated: "The differentiation of organic ureteral stricture and of localized nodal spasm is of prime importance. However, this is frequently difficult and at times impossible." One may consider the following criteria: The reproduction of pain on the passage of a bulb bougie or the injection of fluid is presumptive evidence that the seat of the trouble has been found. Keyser stated that the production of pain in this manner does not differentiate spasm from stricture. The bulb bougie, even though it should hang consistently at the same site, does not differentiate spasm from stricture, as the hang may be due to either. With the patient under a good high spinal anesthesia, however, one expects spasm to abate and organic stricture still to be resistant. This is usually, but not always, the case.

Repeated urography with some form of serial plate taking is important. In most instances stricture will show persistent dilatation above its site, while spasm will be unaccompanied by such dilatation.

At present Keyser uses a three plate pyelographic method in the following manner:

> . . . the first plate being taken in extreme Trendelenburg, the second and third as quickly as possible in reversed Trendelenburg or the upright position. In this way one obtains a serial bilateral retrograde urogram and acquires information as to the mobility of the kidneys as a whole, as well as to the variations of motor activity of the pelvis and ureter. . . .
>
> After thorough ureteral dilatation with bulbs one would expect stricture to remain open longer than would spasm and to produce consequent relief of symptoms for a greater period of time. This, however, is not consistently true, as many spastic ureters are relieved indefinitely after the simple passing of the ureteral catheter. In the ultimate, absolute differentiation of stricture and spasm can be made only by operative or autopsy exposure of the obstructing site.

In considering the therapy of ureteral stricture and spastic reno-ureteral syndromes, Keyser stated:

> The procedures to be considered are the dilatation of the ureter with bulb bearing bougies or catheters; the temporary splinting of the ureter with indwelling catheters; the surgical procedures, such as nephropexy, plastic operations on constricted areas, the resection of hydronephroses, and denervation operations on the renal pedicle or the ureter. . . .
>
> In treating painful reno-ureteric syndromes, ureteral dilatation with bulbs and the use of the indwelling catheter have been the initial effort. I have in recent years used the indwelling catheter more and more, especially at the beginning. . . .
>
> Dilatation is not practiced with acute or subacute infection. Here, if conservative measures of oral antiseptic therapy fail, the indwelling catheter is tried, and successively larger sizes are placed every four or five days. It is

remarkable how severe infection may clear up and what remarkable restoration of renal function ensues with a well draining ureteral catheter.

The indwelling catheter or dilation with bulb bougies has in Keyser's experience given complete to partial symptomatic relief in from 60 to 80 per cent of a large enough series of cases to warrant conclusions. He expressed the belief that conservative ureteral dilation is a method worthy of trial before operation is undertaken, not necessarily because of a high incidence of organic ureteral stricture, but as a therapeutic attempt to readjust an unbalanced neuromotor dysfunction.

Surgical Procedures.—Weiser [25] stated that if the pleura is opened during the course of an operation on the kidney it should be sutured immediately. He advised postoperative evacuation of the pneumothorax with one of the ordinary apparatus for pneumothorax suction by means of puncture and suction. Weiser had had occasion to carry out this procedure with complete success.

Sympathectomy.—Gibson [26] stated that renal sympathectomy produces no harmful effects on the kidney; it is surgically feasible either alone or in conjunction with other procedures, and in a number of conditions there are either relative or definite indications for its application.

Among the indications for renal sympathectomy is some type of renal sympatheticotonia, namely, spasm, atony, dyskinesia, hyperdynamic motility and adynamia, either alone or in association with definite organic changes, such as small hydronephrosis, nephroptosis, painful chronic nephritis, painful adhesive perinephritis, essential hematuria, certain types of Bright's disease associated with oliguria and anuria, unyielding reflex anuria and possibly certain stone-forming diatheses.

Renal sympathectomy is recommended, in conjunction with other necessary surgical procedures, as an extra precautionary measure to make doubly sure of complete relief in any case of proved renal pain in which careful investigation reveals few or no demonstrable pathologic changes to explain the symptoms adequately. Whether renal sympathectomy is undertaken as the primary object of a surgical attack on the kidney or is merely incidental to other procedures, no great technical difficulties are encountered if the precautions necessary for adequate exposure of the kidney are observed. The main bugbear of the operation is the possibility of injury to the renal vein, which is as thin walled as tissue paper. If one bears in mind that the nerve fibrils

25. Weiser, Arthur: Vorschlag zur Behandlung des bei Nierenoperationen durch Pleuraverletzung entstandenen Pneumothorax, Wien. med. Wchnschr. **86:** 1044-1045 (Sept. 5) 1936.

26. Gibson, T. E.: The Present Status of Renal Sympathectomy, J. Urol. **36:** 334-363 (Oct.) 1936.

are in the fascia immediately surrounding the renal artery and if the vein is avoided meticulously except to retract it away from the scene of action, this hazard is appreciably diminished. Experience has shown that the best strategy is to start mesially and work laterally toward the renal hilus. The fascia surrounding the vessels is pushed away with gauze sponges and smooth thumb forceps until the vessels are exposed, and the nerves which are then seen in bundles about the artery are picked up with a hook and resected with scissors. Gibson has found it easier in most cases to start the dissection anteriorly but to perform the major portion of it from the posterior aspect after retracting the ureter and the pelvis with a hernia tape. The artery is approached easily from the posterior aspect, whereas anteriorly it is covered by the vein. A hook is essential in picking up the nerves lying directly on the artery as well as for drawing out the fascia containing the nerves from between the artery and the vein. Great care must be taken that the point of the hook does not touch the vein. A small blood vessel retractor is useful at times in protecting the vein from injury. The dissection should not be carried too close to the renal parenchyma, because often small vessels are given off at this level which are easily broken, thus obscuring the field of operation with troublesome bleeding.

Oldham, after stripping the pedicle as clean as possible, swabbed it with a 10 per cent solution of phenol, which he stated did not injure the vessels or ureter and was strong enough to destroy nerve fibrils missed by the dissection. Phenol also reveals any nerve fibrils that may have been overlooked, and they can then be severed if it is so desired.

Secretion of Urine.—Snapper [27] stated that urine is formed only by the combined action of different physiologic processes in the kidney in which the functions of the glomeruli and tubules are separated completely. It has been proved beyond doubt that in the glomeruli an ultrafiltrate of the blood plasma is formed. The glomerular filtrate contains all crystalloid substances of the blood plasma in the same concentration in which they are present in the blood, but the colloids, especially the proteins, do not pass through the glomerular membrane. In the tubules a reabsorption of water and different substances takes place. During passage through the tubules the original glomerular filtrate is changed into definite urine. The study of the rate of excretion and concentration of certain substances, which pass into the glomerular filtrate, are not reabsorbed in the tubules and are not excreted in the tubules, has shown that an astounding quantity of

27. Snapper, I.: The Pathological Physiology of the Secretion of the Urine, Kong. d. internat. Gesellsch. f. Urol. **6**:575-627 (Sept.) 1936.

glomerular filtrate is filtered off per minute. This quantity varies between 110 and 170 cc. per minute. From 97 to 99 per cent of the water of this glomerular filtrate must be reabsorbed in the tubules. Neither this rate of filtration in the glomeruli nor this excessive reabsorption in the tubules is impossible, as different experiments and calculations have demonstrated. The creatinine and inulin methods by which these data have been obtained have withstood criticism successfully. As a physical ultrafiltration of the blood plasma takes place in the glomeruli, blood pressure must be important for the function of the glomeruli.

The permeability of the glomerular membrane is to be compared with that of a collodion membrane. Substances with a high molecular weight are retained; substances with a low molecular weight pass. As a rule it may be stated that substances with a molecular weight of less than 40,000 appear in the glomerular filtrate, whereas colloids with a molecular weight of more than 60,000 are retained in the blood.

In case of renal insufficiency the composition of the urine and blood may be fundamentally changed. For a normal functioning of the kidneys, a normal composition of the blood plasma is necessary. Changes in the composition of the blood may be followed by serious disturbances of the function of the kidneys, so-called extrarenal uremia. A decrease of the protein content of the blood plasma and of the sodium and chloride content of the blood plasma may both have an adverse influence on renal function. The innervation of the kidney is of great importance in renal function. Reflex anuria may be explained in this way. It is still doubtful whether operations on the nerve supply of the kidneys improve the functions of the diseased kidney.

Urine is a supersaturated solution of many substances. Different substances, practically insoluble, are present in solution of the urine in large quantities. This problem is of great importance in the prevention of the formation of stones. The hydrotropic action of different organic constituents of the urine is considered. Urea and hippuric, salicylic and phenylglycolic (mandelic) acid, and other substances often present in the urine increase the solubility of calcium salts, especially of calcium oxalate. Besides this direct hydrotropic action, the stabilizing influence of these substances on the colloids of the urine is of importance in the prevention of the formation of stones.

URETER

Anomaly.—Malgras [28] said that the extravesical opening of a ureter in the female ordinarily produces a picture of incontinence that is so

28. Malgras, P.: Abouchements extravésicaux de l'uretère chez la femme, J. d'urol. **42**:269-301 (Sept.) 1936.

characteristic that it will immediately suggest the correct diagnosis. It is a permanent incontinence, existing from birth, although micturition is normal. In cases in which the orifice of the ectopic ureter is discovered, retrograde pyelography will make it possible to determine to which kidney it belongs and also will reveal whether there is a double kidney, as is usually the case. Inability to discover such an orifice, however, should not be sufficient grounds for discarding the diagnosis of extravesical ureter if the clinical syndrome is clear. In that case an attempt should be made to demonstrate the abnormal kidney corresponding to this ureter. At present urography seems to be the most precise method for bringing out this evidence, provided more is not demanded of it than it can give. It makes it possible to affirm the existence of a supernumerary pelvis when such an organ is made visible by some opaque medium, but it does not justify the denial of such a pelvis when this is not revealed in the film.

If a double kidney is demonstrated, heminephrectomy is the operation of choice, provided the arrangement of the vascular system permits it. If retrograde pyelography does not determine beyond a doubt to which kidney the ectopic ureter belongs, operative measures will reveal whether, in accordance with Weigert's law, the ureter opening lower down corresponds to the upper pelvis. To obtain this proof, the ureter under suspicion is incised longitudinally, and a catheter is passed from above downward; the point at which the catheter appears at the perineum will then give the site of the ectopic orifice.

Ectopic ureters are particularly prone to be the seat of acute infections which simulate pelvic suppuration of genital origin. Mistaken diagnoses due to this similarity of symptoms have been responsible for many useless laparotomies performed by general surgeons, who have not taken into account the significance of this particular type of incontinence.

Derbes and Dial [29] reported 2 cases of postcaval ureter in man, bringing the total number of cases in the literature to 14. Postcaval ureter in man was first described in 1893. Since then 11 cases have been reported.

These authors observed postcaval ureters in 2 adult cadavers. In each case the lower portion of the right renal pelvis and upper portion of the ureter were dilated and thin walled. The ureter passed behind the inferior vena cava at the level of the third lumbar intervertebral disk, at which point it was definitely constricted. It then passed forward between the aorta and the vena cava and thence downward, forward

29. Derbes, V. J., and Dial, W. A.: Postcaval Ureter: Two Cases, J. Urol. **36**:226-233 (Sept.) 1936.

and laterally across the anterior aspect of the latter vessel. From that point, its course and entrance into the bladder were normal.

In the 14 reported cases, the condition was found in an acardiac fetus, in 2 infants and in 11 adults. Hydronephrosis was present only in the adults, but it was found in all these except 1. In that instance the ureter was encircled by a venous ring at the pelvic brim. It is to be inferred, therefore, that duration is an important factor in the production of hydronephrosis when associated with this anomaly. The hydronephrosis is produced by kinking and stricture attributable to the anomalous course of the ureter, by pressure of the vena cava or by any or all of these factors.

In only 1 of the reported cases was diagnosis of the anomaly made before death, that being made at operation for stone and relief of hydronephrosis. Derbes and Dial stated that they are aware of no way by which a positive preoperative diagnosis can be made, though postcaval ureter should be kept in mind in all cases of hydronephrosis in which the etiology is obscure, as symptoms and sequelae would be similar to those of ureteral obstruction from other causes.

The type of anomaly itself immediately suggests that ureteral dilation or nephropexy will not relieve the hydronephrosis produced by it. If operation becomes necessary and a postcaval ureter is found, a plausible treatment might be transposition of the ureter from its position posterior to the vena cava to an anterior position with ureteropelvic anastomosis.

Calculi.—Grant [30] reviewed 100 cases of ureteral stone and arrived at the following conclusions: A large percentage of stones, probably more than 40 per cent, will pass without any treatment except relaxation of the ureter by medicinal means. Another 45 per cent will pass following ureteral manipulation. Ureteral manipulation, even with catheters, is not without danger. Frequently they cause swelling, which may only increase the obstruction, and perhaps, even more often than is suspected, the ureter may be perforated. Perforation below the stone may not cause any grave disturbances. In the case of infected kidneys, when it is possible to introduce a catheter beyond the stone, indwelling catheter and lavage prior to operation are a decided advantage. Likewise, they enable the surgeon to study the function of the kidney and to determine the choice of operative procedure.

Injury.—Wildbolz [31] proved by an experimental study that if the ends of a ureter which has been cut transversely are properly sutured

30. Grant, Owsley: Cautions in the Treatment of Ureteral Calculi, Ann. Surg. **103**:935-940 (June) 1936.

31. Wildbolz, Egon: Die quere Ureternaht und ihre Folgen. Experimentelle Studie, Ztschr. f. urol. Chir. u. Gynäk. **42**:56-79, 1936.

together so that stricture does not occur, the ureter resumes its functions and that the kidney above the anastomosis functions normally. Considerable experimental work has been done on this subject, all of which suggests that hydronephrosis develops above the line of suture. Most of the experimental animals have been killed several days or weeks after operation in order to examine the kidneys, and most of the various investigators have concluded that hydronephrosis was developing because of dilatation of the ureter and pelvis above the line of suture. In most of these experiments the ability of the ureter to hypertrophy had been overlooked.

Wildbolz in his experiments exposed the ureter through a transperitoneal incision, cut it through just below the renal pelvis, resutured the ends together with a circular suture and closed the wound without drainage. This procedure was carried out on 11 dogs. One died the day after operation and 1 a month later. In neither was there infection of the field of operation. A pyelogram was made every six months on the remaining dogs, which were in excellent physical condition. The dogs were killed at the end of two years. In 4 a stricture of the ureter was found at the point of suture, and above that marked hydronephrosis had developed. This hydronephrosis could also be seen in the pyelograms. In 5 dogs good results were obtained. The kidney above the suture was normal, and there was no atrophy of the parenchyma on microscopic examination. The ureter above the suture was dilated, as was also the pelvis in some of the dogs. The wall of the ureter and pelvis was always thickened and the muscularis hypertrophic.

In conclusion, Wildbolz stated that suturing of the transversely cut ureter when properly done does not always cause hydronephrosis. This procedure could readily be used in surgical work in cases in which it is necessary to cut the ureter or it is cut accidentally.

Transplantation.—Hinman and his associates,[32] from a study of uretero-intestinal implantation, stated that peritonitis rarely occurs as a result of contamination by the contents of the bowel or by urine at the time of operation when obvious precautions are followed. Leakage from the bowel or the ureters after operation is the common cause of peritonitis. Leakage occurs when the anastomosis is faulty and the ureter has not been sutured securely into the opening of the intestine, when anchoring sutures tear or slough out, when a suture punctures the bowel (fecal fistula) or the ureter (urinary fistula) and on necrosis of a portion of the intestine or of the transmural portion of the ureter.

32. Hinman, Frank; Murphy, W. K.; Wyman, Brent; McCorkle, H. J., and Benteen, F. H.: An Experimental Study of Uretero-Intestinal Implantation, Surg., Gynec. & Obst. **62**:909-917 (June) 1936.

The blood supply of the bowel or ureter must not be tied off by sutures or impaired by too great constriction, which may occur when suturing is done in layers.

Infection of the abdominal wound from contamination at the time of operation is more likely to result than peritonitis. Abscesses in the abdominal wall may rupture to the inside and produce peritonitis.

Implantation by any method which requires that the bowel be opened at the time carries considerable risk of localized inflammation of both the bowel and the ureter. Localized peritonitis may clear up or become general. An abscess may be absorbed, or it may rupture into the cavity and then produce peritonitis. Periureteritis may produce urinary obstruction, or the infection may ascend to the kidney. Localized inflammation may lead to anemic necrosis of the bowel or ureter, leakage and, ultimately, peritonitis. Inflammation at the site of implantation may result from temporary leakage after operation, and this probably is the most frequent cause.

Counseller [33] has found that the satisfactory results that have been obtained after transplantation of both ureters to the pelvic portion of the colon for exstrophy of the bladder have formed a stimulus for similar surgical treatment of women when the urinary bladder has been rendered useless by traumatism or disease. Counseller in his article refers particularly to huge vesicovaginal fistulas, chronic interstitial cystitis with secondary contraction of the bladder and certain carcinomas of the bladder.

The surgical technic employed follows the principles of C. H. Mayo and Coffey. The right ureter is transplanted first, and the left ureter, not earlier than two weeks later. Thirteen illustrative cases are reviewed briefly. There were three deaths. As the urinary bladder is obviously the best receptacle for urine, bilateral uretero-enterostomy should not be undertaken without serious consideration of all circumstances in each case. Surgical risk is minimized by giving attention to the general condition of the patient; the status of the upper part of the urinary tract, with regard to the presence of obstruction, infection or reduced function of the kidneys; the presence or absence of pelvic cellulitis which involves the lower ends of the ureters; previous surgical procedures on the pelvis, which may have resulted in fixation of the important structures, and the preoperative preparation of the patient. The risk of operation is definitely increased if one attempts to transplant grossly abnormal ureters to the bowel. At times preliminary nephrostomy may be utilized as a procedure to reduce infection and

33. Counseller, V. S.: Bilateral Transplantation of the Ureters of the Female, Proc. Staff Meet., Mayo Clin. **11**:699-701 (Oct. 28) 1936.

relieve obstruction to the kidneys prior to ureteral transplantation. Occasionally such a procedure is necessary after treatment of carcinoma of the uterine cervix with radium. Intravenous urography is definitely helpful in determining the status of the kidneys prior to operation.

PROSTATE GLAND

Prostatectomy.—Schanz [34] reported 323 new cases in which operation has been performed by Kirschner since 1931. In the total group of 745 cases, there were 574 of adenomatous hypertrophy of the prostate gland. Most of the patients were in poor general health when first seen.

Radical operation was performed on all the patients who were strong enough. Kirschner preferred the perineal route and gave the following reasons for this: When prostatectomy is performed by the suprapubic route, the bladder must be opened twice, and also the prostate gland is situated much deeper than when the perineal approach is employed. The perineal method avoids opening the abdomen and thus diminishes the incidence of pulmonary complications. Bleeding can be controlled easier, and there is no need for a packing. The secretions from the incision drain more readily from the perineal wound than from the suprapubic, and the sphincter muscles can be preserved more readily. In 292 (51 per cent) of Kirschner's cases the perineal route was employed. The mortality was 4.2 per cent, and the results at the time of the patient's dismissal and on reexamination from one to four years later were the best of all methods of treatment. Contraindications to the radical operation are serious disturbances of the circulation or renal function, cachexia, diabetes and perivesical infection.

For the patients who were comparatively well but who could not stand radical operation, suprapubic drainage was instituted. This was the treatment until 1932 and was employed in 94 cases (7 per cent). Since then the patients who could not stand radical operation had been treated by transurethral electroresection; this was used in 42 cases (7 per cent). The great disadvantage of transurethral methods is the risk of leaving a malignant prostate gland without realizing it. Schanz estimated this risk at about 15 per cent. That is the principal reason why Kirschner preferred radical operation. There were 4 deaths (12 per cent) after transurethral electroresection. The results were not as good as those of perineal prostatectomy. The high mortality is due to the fact that all the patients in good general condition underwent prostatectomy.

34. Schanz, F. E.: Ueber Behandlung und Behandlungserfolge des Prostataadenoms, Ztschr. f. urol. Chir. u. Gynäk. 42:169-198, 1936.

One hundred and forty-six patients (26 per cent) were too ill to undergo any operative intervention. For the permanent treatment of inoperable conditions, the indwelling catheter in the urethra is superior to suprapubic drainage. The catheter that is put in after ligation of the vas deferens to prevent epididymitis can be worn for years if properly cared for. Most of the patients on whom suprapubic drainage was instituted were uncomfortable and dissatisfied.

Haim [35] stressed the superiority of perineal prostatectomy over all other procedures. He stated that there are only two reasons why it is not used as widely as it deserves: The technic is more difficult, and surgeons who employ the suprapubic method, which is easier to do, are diffident. The advantages of the perineal method are that less shock and fewer cardiac and pulmonary complications result and that there is a reduction in the number of cases of thrombosis and embolism.

To increase the use of perineal prostatectomy, Haim recommended standardizing and simplifying the procedure in order to rule out the possibility of postoperative incontinence and fistulas. These complications occur rarely in the hands of a surgeon skilled in perineal prostatectomy, and when they do occur it is usually in cases of carcinoma. He recommended going in between the anal sphincter and the rectal wall, so that the rectum may be seen during the operation, and the injection of some fluid into the prostate gland between the adenoma and the capsule to make enucleation easier.

Lumb [36] reported a technic for suprapubic prostatectomy, its main advantages being the facility with which the floor of the bladder can be reformed and the definite approximation of trigonal tissue to the divided posterior urethra. After an extended trial, this operation has fulfilled its purpose, and its value is enhanced by its simplicity, since complicated instruments and illuminated retractors are not needed for its performance.

Several advantages have resulted from this method: The trigonal flap is stretched evenly over as large a portion of the posterior aspect of the prostatic cavity as it can be made to cover. There is maximal approximation of the trigon to the posterior urethra, intimate contact between the whole of the trigonal flap and the underlying wall of the prostatic cavity and reduction of hemorrhage. The floor of the bladder, when reformed, closely approximates normal.

A gum elastic coude catheter having two eyes is threaded with two moderately stout silk threads about 18 inches (46 cm.) long, so

35. Haim, Emil: Gedanken zur Behandlung der Prostatahypertrophie, Wien. med. Wchnschr. **86**:1004-1007 (Sept. 5) 1936.

36. Lumb, Norman: Trigonal Loop-Traction in Suprapubic Prostatectomy, Brit. J. Urol. **8**:257-265 (Sept.) 1936.

arranged that about 3 inches (7.6 cm.) of each projects from each eye. The catheter is passed into the bladder, and the distending fluid is injected. A wooden spigot closes the catheter, and a sterile towel is arranged on which the outer ends of the silk threads rest beside the catheter. A pair of small artery forceps is attached to one thread and a pair of large forceps to the other, so that the threads may be distinguished subsequently, or silk threads of different color may be used.

A midline incision is preferred, though a transverse one may be adopted equally well; the peritoneum is displaced gently upward, exposing the bladder, which is opened at its highest point. The wall of the bladder is punctured, and a suction tube is used to evacuate the contents. Great care is taken to avoid opening the cellular tissue in front of the bladder.

The ends of the two silk threads which are in the bladder are unthreaded from the eye of the catheter; a small forceps is placed on one and a large forceps on the other, and the catheter is withdrawn. Two separate silk threads thus traverse the urethra from the meatus to the bladder. The prostate is enucleated as expeditiously as possible. Dry gauze from a 3 inch roll is lightly packed into the cavity to check hemorrhage. A self-retaining retractor is inserted, and the gauze is withdrawn.

A fine silk suture, 18 inches long, is made through the trigon in the middle line, about ½ inch (1.3 cm.) behind the raw edge, thus securing a firm hold on it. The ends of the suture material are tied to the bladder end of one of the silk threads previously mentioned and drawn through the urethra to the external meatus. When the threads are pulled tight a triangular flap of trigon is drawn down, largely obliterating the posterior portion of the prostatic cavity and diminishing the bleeding. The weight of the forceps attached to the silk thread will be found sufficient to keep the flap in position at this stage, and the indwelling catheter is inserted next. A flute-ended india rubber catheter, size 22, with two lateral openings, is used for this purpose. After lubrication it is readily drawn into the bladder by the second silk thread, which is secured to its tip. The silk thread is removed, and a stout silkworm gut stitch is attached instead to the tip of the catheter, the ends being held in a forceps. This is used later for suspending the catheter in its final position within the bladder.

At this stage bleeding is considerably diminished, and the remainder of the plastic portion of the operation consists in inserting the anterior obliterating stitches. These may be made more effective by using the infolding method to be described, as they then tend to diminish pocketing in the anterior part of the cavity during healing. A wide hold is

taken with the boomerang needle, and the catgut stitch is drawn through. The two free ends of catgut are made to cross to opposite sides of the prostatic cavity, where each is threaded on a needle, a portion of the rim is picked up and the ends emerge once more into the bladder. On tying the ends, infolding takes place and the edges are well inverted.

The catheter is carefully adjusted so that its lower lateral eye lies just at the entrance to the torn posterior urethra, thus draining the prostatic cavity completely, and a small drainage tube is placed in the bladder. Closure of the wound in the bladder is carried out in the usual way, with an inverting stitch, followed by a second layer of fine catgut. The drainage tube should lie at the upper end of the incision into the bladder and be firmly gripped; the loop of silkworm gut suspending the catheter emerges immediately below it. The catheter is left in place for from ten to twelve days and then removed, together with the traction stitch from the trigon.

Resection.—Thompson and Buchtel [37] reported a series of 200 consecutive cases of prostatic hypertrophy in which treatment involved transurethral resection of 25 Gm. or more of prostatic tissue; 140 patients, or 70 per cent, had suffered from complete urinary retention. Eighty-eight patients, or 44 per cent, were aged 70 years or more.

Thorough removal of all adenomatous tissue which encroaches on the neck of the bladder, particularly in the anterior half, so that all inverted V deformity is eliminated, and careful hemostasis during the progress of the operation are important points in technic. An operation must not be prolonged or shock may result; in Thompson and Buchtel's experience, patients withstand a two stage or three stage procedure, each of short duration, much better than a single operation which lasts more than one hour. The bladder must not be allowed to become overdistended at any time during operation or during the postoperative course or fever may ensue. If the functional result is not good immediately after drainage by inlying catheter has been discontinued, judicious intermittent catheterization or early reoperation is essential to an uncomplicated convalescence.

Replies to letters of inquiry indicate a high degree of satisfaction among the patients. Sixteen patients (15 with benign lesions and 1 with a malignant lesion) have returned to the clinic for reoperation six months or more after their dismissal. One of these patients was subjected to perineal prostatectomy, while the others preferred to undergo further transurethral resection. The mortality in the series was 1.5 per cent.

37. Thompson, G. J., and Buchtel, Henry: Transurethral Resection of the Large Prostate: Review of Two Hundred Cases in Which Twenty-Five Grams or More of Tissue Was Removed, J. Urol. 36:43-56 (July) 1936.

It occurred to Emmett [38] that because of the hemostatic quality of posterior pituitary it might be of value in the reduction of hemorrhage in transurethral resection of the prostate gland. Resection at the Mayo Clinic is performed by means of the direct vision, cold-cutting resectoscope, in which an electric current is employed only to fulgurate individual bleeding points after tissue has been removed by the tubular knife. Because of the fact that a lens system is not employed, bleeding causes little difficulty with vision. However, it is important that as little blood as possible be lost during and after the operation; hence, any method that might aid in conservation of blood is worthy of investigation.

A rigid needle has been constructed, with a shaft long enough to project through the full length of a Braasch direct vision cystoscope. The needle proper is of 21 gage and is ⅞ inch (2 cm.) in length; it has a small, circular hilt where it joins the shaft to prevent it from being inserted any farther than its length into the prostatic tissue. At operation an injection is made into each of the three prostatic lobes. To make the injection, the heel of the cystoscope is placed against the portion of the lobe into which the solution of posterior pituitary is to be injected, and the cystoscope is maneuvered so that it forms, as nearly as possible, a right angle with the surface of the lobe. This is done in order to assure the injection of material well into the tissue rather than just having the needle slide under the mucosa. This is the most difficult part of the technic of the injection. The needle is then introduced blindly, as one implants radon seeds, and is inserted into prostatic tissue to the hilt. A third of the total dose of posterior pituitary is injected into each lobe. A total injection of from 1 to 3 cc. of solution of posterior pituitary of double U. S. P. strength has been used, but 2 cc. seems to be about the proper amount. In 2 cases a mixture of 1 cc. of solution of posterior pituitary and 1 cc. of ergotamine tartrate was used.

In 31 consecutive cases in which resection of the prostate gland was performed, the foregoing method of injection was employed. Spinal anesthesia was used in all the cases. In 29 cases injections of solution of posterior pituitary alone were given, the total dose varying from 1 to 3 cc., whereas in 2, injection of a combination of 1 cc. of solution of posterior pituitary and 1 cc. of ergotamine tartrate was employed.

Results of injection are interesting. In 25 cases results were satisfactory; in 7 of these no bleeding was encountered at the operation,

38. Emmett, J. L.: Preoperative Intraprostatic Injection of Pituitrin in Transurethral Resection: Preliminary Report, Proc. Staff Meet., Mayo Clin. **11:** 619-622 (Sept. 23) 1936.

which was terminated within thirty or thirty-five minutes. In the remaining 18 cases the wash water was colorless for periods varying from twenty-two to forty-seven minutes. The average length of time for the water to remain clear was about twenty-seven minutes. In these cases, after this period vessels began to bleed in varying degrees from slight to rather sharp bleeding. All bleeding was easily controlled with the usual fulguration. In the remaining 6 cases, experience in which was not classed as satisfactory, the results were as follows: In 2 they were fair; that is, at no period was the wash water absolutely colorless, but instead it was only a light pink for about twenty to twenty-five minutes, after which the usual bleeding occurred; in 1 of the remaining 4 the wash water was colorless for ten minutes, and then moderate bleeding occurred, while in the other 3 it was difficult to say whether the posterior pituitary had any effect.

Kretschmer [39] stated that his position in the discussion of transurethral resection can best be summarized by saying that during the past fifty-one months he performed prostatectomy only once and that during the same time he refused resection to only 1 patient.

The period of hospitalization is much shorter with resection than it is with surgical prostatectomy, and while this fact may not be of much importance to a small percentage of patients, all things being equal, it is an economic factor of enough importance to demand attention.

The number of cases in which preliminary suprapubic cystostomy is employed has become fewer and fewer. During the past three months preliminary cystostomy has been done only once. On the other hand, Kretschmer expressed the belief that cystostomy is indicated when drainage by catheter fails because of chills, fever, pain or bleeding, or when small stones with severe infection or large stones are present.

The number of patients with cardiac conditions seeking relief has increased definitely. Whereas, in the days of surgical prostatectomy about 35.8 per cent of the patients suffered from cardiovascular lesions, a recent study of Kretschmer's cases in which resection was performed revealed cardiovascular lesions in 64.3 per cent, an increase of 28.5 per cent.

As Kretschmer's experience with resection widened, he performed operation in a certain group of cases without preliminary drainage by catheter. Heretofore all patients who had 4 ounces or more (120 cc.) of residual urine were given preliminary drainage. At present no preliminary drainage is employed in a case in which the residual urine does not exceed 6 ounces (180 cc.), provided the urine is clear, the

39. Kretschmer, H. L.: Transurethral Resection, Ann. Surg. **104**:917-933 (Nov.) 1936.

renal function normal and the heart and lungs in good condition. Preliminary cystoscopy is no longer carried out as a routine; once the diagnosis of prostatic obstruction has been made, the type of enlargement is determined when resection is performed. The exceptions to this rule are: in case the history is not typical for prostatic obstruction, if there is a history of one or more attacks of hematuria and if the cystogram reveals a filling defect.

In Kretschmer's series of cases in which resection was done, a second resection was performed in 10.6 per cent and a third one in 3.7 per cent.

Before the technic of resection was completely mastered, hemorrhage at operation was at times a serious problem, but with experience this untoward occurrence has become less of a problem, although occasionally a serious hemorrhage occurs no matter how careful one is. Careful search for the bleeding point should be made and its immediate control effected. Secondary bleeding, which was never severe, occurred in 19 cases on the tenth to the fourteenth day. Clots, when present, were evacuated with the Bigelow pump, and the bladder was washed out with a warm solution of silver nitrate. In most of the cases this controlled the bleeding, but when this procedure failed the resectoscope was introduced, and the bleeding point was fulgurated or excised. Late hemorrhage occurred in 14 cases at periods varying from three months to two years after resection. In the patients who were reexamined, enlarged vessels were found around the orifice of the bladder and in the prostatic urethra. These were destroyed by fulguration. An interesting fact is that these late hemorrhages occurred in patients with large prostate glands.

The incidence of epididymitis has diminished as experience with resection has grown. In 15 per cent of the first 117 cases this complication occurred, and vasectomy was done as a routine, an operation no longer employed, as this complication is very rare.

There has been no instance of complete incontinence in Kretschmer's series of 804 cases in which resection was performed. Shortly after leaving the hospital a small number of patients have had difficulty in holding urine. This was due not to incontinence but to urgency and imperative urination. Continence of urine was eventually recovered. In a few instances the patients would lose a few drops, but this was temporary, and as the infection cleared up the condition rapidly disappeared. In 2 instances the loss of a few drops of urine was due not to incontinence but to st icture of the urethra.

The mortality has fluctuated from time to time, depending in part on the type of cases and whether or not one wishes to refuse resection to many of the patients who are considered bad risks, which Kretschmer

has not done. His records show that he has performed 184 resections with but 1 death—a mortality of 0.54 per cent. The 804 patients who were operated on included a large number who were classed as bad risks, and the mortality for the entire series was 3.9 per cent.

Beer [40] stated that these new methods of transurethral resection are of use in the following conditions:

1. Contractures of the neck of the bladder, which in years past were excised by a wedge-shaped excision from above through the bladder. These can be cut with a point or loop electrode, an ordinary operating cystoscope or a resectoscope being used. Complete relief from symptoms results. This is a great improvement over the cold punch operation or the suprapubic excision. The latter procedure or approach, however, may be useful when the exact physical status of the neck of the bladder is not accurately visualized.

2. Obstruction caused by carcinoma of the prostate gland. This condition also lends itself satisfactorily to transurethral resection, which may be repeated as a new obstruction develops. The tissue removed during such an operation is often helpful in establishing the correct diagnosis.

3. The ordinary and usual type of prostatic hypertrophy or adenoma. When it comes to these conditions the field of transurethral resection has no limitations for some enthusiasts and definite limitations for others. Included here as a subgroup is moderate prostatic enlargement associated with mild symptoms of frequency and questionable obstruction and a small amount of residual urine. No experienced surgeon would feel justified in performing prostatectomy on a patient with a condition of this type. Such patients present a definite potential field for transurethral resection and may represent a large proportion of the total in most published series of resections. The frequency, and perhaps the infection, do not always disappear but may be made worse after excision of some prostatic tissue, despite a reduction of the residual urine. In these cases the lesion is definitely a beginning prostatic adenoma and is not to be considered with those cases in which prophylactic resection has been performed before any definite complaint has developed. It is doubtful whether resection affords the patient the expected relief with any regularity. If the subjective complaints are well developed, one is justified in attempting to give relief by resection, even though it may be only temporary and incomplete. Correct diagnosis here, as always, is essential.

In addition to those patients with mild symptoms referable to the prostate gland who frequently are worse off after resection, there are

40. Beer, Edwin, in discussion on Kretschmer,[39] pp. 928-931.

two other groups of patients who have definite prostatic adenoma that must be discussed: those with moderately large, bilobed, trilobed or single lobed prostate, and those with large, more or less trilobed or bilobed hypertrophy. In localities in which no pressure is brought to bear on the surgeon by competitors, the patient or his friends, the opinion is gradually developing that the last-mentioned group, with large, succulent adenomas, should be treated radically and definitively by prostatectomy or enucleation of the adenoma, either by the suprapubic or by the perineal approach. This attitude seems to be based on a great many factors, without denying that if the "resectionist" is patient he can whittle away a fair amount of the largest prostate in one or more sessions.

The two stage suprapubic prostatectomy has gradually assumed the status of an almost minor procedure, with a low mortality, of 6 + per cent, which is usually incidental to cardiovascular disturbances, and with complete cure without chance of recurrence, if properly performed. On the other hand, the transurethral approach for the large adenoma frequently is followed by a whole group of complications, such as primary or secondary hemorrhage into the bladder, which necessitates repeated evacuation of clots, infection of the bladder and more or less complete resection of the base of the prostate gland which frequently, much more frequently than is reported, may turn the scales against the patient, not to mention the various instrumental damages and perforations that are reported by competent instrumentalists. Because of the prolongation of the necessary instrumental work and the various complications, the mortality is likely to be definitely higher than with the transurethral approach with a two stage suprapubic enucleation. This is Beer's experience. He stated that if the statistics on prostatic adenoma alone were considered, the data of other clinics would probably bear him out. The trouble with most statistical studies along these lines is that they include the results of operation for simple contracture, small, almost symptomless hypertrophy and moderate-sized but definite adenoma of the prostate gland as well as extensive hypertrophy and of prophylactic excisions, done perhaps because of incorrect interpretation cystoscopically.

In the moderately enlarged prostates, as opposed to the very large adenomas, which weigh an ounce (28 Gm.) or more and are as large as one to three or more lemons, there is a definite field of usefulness for transurethral resection, even though repeated sessions may be required before the patient can void and be comfortable and even though, as time goes on, one may see more and more of these partially removed adenomas redevelop and produce recurring symptoms, which is a rare sequela to a properly executed complete enucleation. There is no doubt

that in this group of moderately enlarged prostates one is justified in using transurethral resection, if the patient requests it and especially if he is a poor surgical risk because of poor renal function, coronary disease, diabetes, etc.

According to Beer, a careful follow-up of the cases in which resection was done leaves much to be desired.

Beer stated that he was impressed by the reports of large numbers of cases in which resection has been performed and yet continued treatment, soundings, irrigations of the bladder, etc., are necessary; these are practically never required when a proper prostatectomy has been performed. There is no doubt that most patients void more readily after resection and have much less residual urine than before the operation, but a large number of patients are not absolutely and definitely cured, as they are after a complete enucleation of the adenoma. Pyuria, frequency and dysuria often persist for months or permanently in every series of cases in which a really careful check is maintained.

That transurethral resection of the prostate gland has become an unusually popular procedure, without due selection of cases, cannot be denied.

Lower [41] stated that transurethral resection of the neck of the bladder for obstruction has been revived in the last few years, probably because of improvements in instruments and electrical apparatus. Not only are the median bars and the sclerotic obstructions resected now, but the use of transurethral resection is being extended to include a much wider field, especially in the treatment of prostatic hypertrophy.

In what cases should this procedure be used? Experience has taught that its scope of usefulness is much wider than was formerly thought, but again the danger of broadcasting the simplicity of the operation should be emphasized. However, it is true that it carries with it a low mortality, and so far the postoperative results in most cases have been good. Among approximately 500 resections which have been performed at Lower's Clinic, the mortality has been 1.8 per cent, including a series of 225 cases in which no deaths occurred. These were not selected cases, but included all types. Among the patients were many feeble and elderly persons.

As wider experience has been gained, larger and larger amounts of tissue have been removed. Another advantage of this operation is that a second or even a third operation may be performed if necessary without any special risk.

Bleeding is becoming inconsequential. When the procedure was first used, bleeding occurred frequently, but Lower has found it necessary to open the bladder in only 1 case.

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41. Lower, W. E., in discussion on Kretschmer,[39] pp. 931-932.

The incidence of epididymitis in the entire series was 6.8 per cent, and the average stay in the hospital was less than seven days; this economic factor is of considerable importance, especially in these times.

Cabot [42] stated that in the first place there are various methods of whittling out the prostate through the urethra. His notion is that the instruments will probably be greatly modified. The problem should be discussed without prejudice. Beer has perhaps a case to prove; he performs chiefly prostatectomy. Kretschmer has a case to prove; he does chiefly resection. Cabot stated that he has no case to prove.

In reference to Beer's remarks on the unfortunate results of resection, Cabot stated that if the truth were told, the statistics would be loaded handsomely with the unfortunate results of prostatectomy. The mortality of prostatectomy, which up to the last few years was over 50 per cent in the hands of the occasional surgeon, has never been less than 20 per cent the country over, and is not now. Prostatectomy is an operation for experts, whether the suprapubic, the transurethral or the perineal method is used. The discussions should be confined to the results obtained by experts, not to the results obtained by surgeons who operate on the patient not for prostatic obstruction but for a hundred dollars. That will cause damage, and does, in every field of surgery. It is not fair to the operation.

Six years ago, more than half the patients on Cabot's surgical list were to have prostatectomies, but he has not done a prostatectomy in three years. There have been only 3 or 4 done in the last two years at the Mayo Clinic.

The age group is interesting. Of 1,922 consecutive prostatectomies done between 1924 and 1932, 5.6 per cent were performed on patients more than 75 years of age. Of the last 700 transurethral resections done up to Jan. 1, 1936, 15.7 per cent were performed on patients over 75.

It is frequently suggested that this operation is being performed chiefly for patients who do not need it, which is not entirely true. Patients who are more gravely ill are being operated on with better results.

It has been the habit at the Mayo Clinic, and it is not a bad one, to keep all the tissue which the surgeon removes. About a year ago Cabot thought that it would be interesting in a series of 1,000 cases to take a fair average of the gross amount of prostatic tissue removed by suprapubic prostatectomy and to compare it with the gross amount removed by transurethral resection. The amounts removed by resection are approaching those removed by prostatectomy. The group of men at the Mayo Clinic who perform resections now take out almost as

42. Cabot, Hugh, in discussion on Kretschmer,[39] p. 932.

much tissue on the average as was taken out by prostatectomy five years ago. It thus appears that the transurethral route is becoming the method of prostatectomy. If the same amount of skill for this method is insisted on as is shown by the experts using the suprapubic or the perineal route, resection has much to offer and will cover a large portion of the field.

Carcinoma.—Chauvin and Mosinger [43] asserted that the histogenesis of malpighian tumors of the prostate and other viscera which, like the prostate, possess no paramalpighian structure, is a subject of the greatest interest and that three hypotheses have been suggested to account for it. 1. The tumor develops on an island of malpighian metaplasia, such as can be observed in the biliary and respiratory tracts and in the body of the uterus after a chronic inflammatory process. 2. The tumor develops on a dysembryoplastic soil. 3. It is the result of the direct transformation of normal epithelium into a cancerous tissue of malpighian structure.

In order to choose among these hypotheses, the authors undertook to discover the relative frequency of malpighian or paramalpighian islands in nontumorous prostates, in adenomas of the prostate and in epitheliomas in which glandular substance predominates. In a malpighian epithelioma of the prostate they found an adenomatous zone and an epitheliomatous zone, the latter in the center of the former. They were thus able to prove the coexistence of an adenomyoma of the prostate in which the hyperplastic process was doubled by the phenomenon of malpighian metaplasia and a malpighian epithelioma grafted on the adenomyoma.

It might have been thought, in view of the frequency of a malpighian metaplastic process in the purely adenomatous zone, that the epithelioma developed from a malpighian island. But a study of the epitheliomatous zone revealed conclusively that metaplastic malpighian trabeculae could arise directly from epithelial tubes that were themselves tumorous. Chauvin and Mosinger were able to demonstrate beyond a doubt the truth of the third hypothesis, that of immediate tumor metaplasia; but that this process occurs in a predisposed territory was shown by the frequency of metaplastic islands disseminated in the adenomatous zone. In nontumorous prostates in which there was chronic prostatitis, they found islands of malpighian metaplasia developing often in contact with islands of inflammatory connective tissue. Of 6 prostatic epitheliomas of various structures, they observed malpighian islands lying in the midst of the tumor tissue in 3.

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43. Chauvin, E., and Mosinger, M.: Sur les épithéliomas malpighiens de la prostate et leur histogénèse, J. d'urol. **41**:297-306 (April) 1936.

They concluded that malpighian metaplasia is observed in 32 per cent of cases of adenoma of the prostate and in an equal percentage of cases of prostatitis. The possibility of malpighian cancers developing secondarily from these islands must then be faced. However, the study of their own case of malpighian cancer and the frequency of malpighian islands in cancers of the prostate of different structure show that the malpighian aspect may appear even at the moment of canceration.

Uebelhör [44] stated that fairly uniform results are obtained in most clinics in the treatment of carcinoma of the prostate; namely, only a few lasting cures are obtained, but there is improvement in many cases.

The first question that Uebelhör discussed is: Why do so few surgeons use the perineal method, when Young and Wildbolz get such good results? The answer is easy; most surgeons use the suprapubic approach as a routine procedure, and when they perform perineal prostatectomy occasionally for carcinoma they have a great percentage of fistulas, incontinence and strictures, which discredits the method in their eyes. Uebelhör and the representatives of the Viennese school prefer the suprapubic route for prostatectomy, but Uebelhör expressed the belief that it would be wise to practice the perineal method also in order to be able to use it with success in suitable cases.

Radical operations have not found many followers. The shock to the patients is too great, and the chances of freedom from cancer are too unstable. Suprapubic drainage is not "the best of all methods" in these cases, as has often been quoted. Its use is justified only in cases of obstruction, in which it is competing successfully with transurethral resection. Uebelhör stated that roentgen therapy according to the Coutard technic or radium therapy in combination with surgical intervention is the most promising method. The remarkable variations in the course of the disease make estimation of the value of any new method of treatment difficult; for example, occasional patients survive more than four years after a definite diagnosis of carcinoma has been made, even in the absence of treatment.

Keyes and Ferguson [45] argued that the term "early" as applied to prostatic carcinoma covers that group of cases in which diagnosis cannot be made by rectal examination. The disease surely exists before it is palpable by rectum. There have been cures when the malignant growth was confined to a hypertrophied portion of the gland and the patient was fortunate enough to have undergone prostatectomy for the relief of the enlargement. The carcinoma, not having extended to the remain-

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44. Uebelhör, Richard: Bemerkungen zur Therapie des Prostatakarzinoms, Wien. med. Wchnschr. **86**:1038-1044 (Sept. 5) 1936.

45. Keyes, E. L., and Ferguson, R. S.: Early Diagnosis and Radical Treatment of Carcinoma of the Prostate, Brit. J. Urol. **8**:346-352 (Dec.) 1936.

der of the gland, comes out with the adenoma, and its presence is unsuspected until shown on pathologic section.

Because of the difficulties of recognition of this "early" prostatic carcinoma, Keyes and Ferguson removed material for biopsy by aspiration from all prostates in men aged more than 50 years whose glands were the least bit irregular. They reported on 2 series of cases in which biopsy specimens were secured in this manner. In the first series, consisting of 100 cases, biopsy was done by Ferguson at the Memorial Hospital. In 18 of the cases insufficient tissue was obtained to permit a diagnosis. In 59 of the others a diagnosis of carcinoma was made, and in 23 the tissue was found to be noncarcinomatous. Fifty-seven patients in whose prostates carcinoma was found have died of carcinoma. One of the survivors is living, but metastasis has occurred, and the other, who submitted to interstitial irradiation by the Ferguson technic, is alive and well. Those patients whose tissue was pronounced to be noncarcinomatous have remained free from the disease to date.

In a similar series of 33 cases in which tyros undertook to perform biopsy on specimens obtained by aspiration, no tissue or insufficient tissue was obtained in the first 14 cases, and the pathologist was not able to distinguish carcinoma until the twenty-fourth specimen. After that he found tumor cells in 10 cases in succession. As in the first series, in no case in which the specimen was reported as noncarcinomatous are symptoms of carcinoma of the prostate known to have developed.

The method employed by the authors for the radical treatment of carcinoma of the prostate is the implantation of gold radon seeds (each containing 2 millicuries of the radium emanation) into the tumor by means of an instrument devised by Ferguson. This permits the accurate placing of the seeds, the urethral and vesical mucosa and the normal tissues about the tumor being avoided.

Since first using this method in May 1931, Ferguson has studied 41 patients treated by his technic by himself and others. He groups them according to results as follows: "rectal touch doubtful, biopsy positive," 14 patients, 9 of whom are alive and well, 4 for more than three years; "touch and biopsy both positive," 27 patients, 4 of whom are alive and well from one to two years. The authors stated that this procedure, with its low mortality, promises to compare favorably with the total prostatectomy of Young.

Nitch [46] stated that conservative treatment of carcinoma of the prostate comprises radiotherapy, surgical procedures and surgical procedures combined with radiotherapy.

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46. Nitch, C. A. R.: The Conservative Treatment of Carcinoma of the Prostate, Kong. d. internat. Gesellsch. f. Urol. **6**:147-154 (Sept.) 1936.

The immediate results of roentgen treatment are often excellent, but the ultimate results are disappointing. In some cases the roentgen rays cause a rapid increase of the growth and dissemination. The best results are obtained by the five field maximal method of Holfelder-Reisner with a total depth dose of from 150 to 200 per cent on the prostate. The intensive split dose method of Levitt, now under trial, seems productive of better results. At present only 6 per cent of cures can be claimed for modern methods of roentgen therapy. The results of radium therapy are better, especially when applied in large doses to the rectal, vesical and urethral surfaces of the prostate. Before treatment is begun, a thorough clinical, biochemical and roentgenographic examination must be made, and a portion of the prostate should be removed by electroresection for microscopic examination. About 70 mg. of radium is used in the treatment as follows: Fourteen milligrams is applied to the posterolateral surfaces, 50 mg. to the vesical surface and 5 mg. to the urethral surface. Though only a few patients have been treated in this way, the percentage of cures has been 28 up to the present. The method is therefore worthy of an extended trial. When results of renal function tests are below normal, preliminary drainage of the bladder is necessary.

Conservative surgical treatment consists of suprapubic drainage, transplantation of the ureters and electroresection. Transplantation of the ureters into the large intestine is preferable to suprapubic drainage but can be performed only in carefully selected cases.

Electroresection is the best palliative measure for the relief of obstruction caused by growth at the neck of the bladder. It is of no value when the obstruction is due to invasion of the prostatic urethra. It is probable that in the future electroresection followed by some form of radiotherapy will be the method of choice in treatment of carcinoma of the prostate.

Schanz [47] recorded Kirschner's experience of nineteen years in the treatment of diseases of the prostate in surgical clinics of Königsberg, Tübingen and Heidelberg and reported the results of surgical treatment in 144 cases of prostatic carcinoma. He stated that the radical perineal operation is the ideal treatment for a prostatic malignant condition and is the only method that offers a possibility of permanent cure. Operation is performed only when the patient is in good general condition and when the growth has not extended beyond the prostatic capsule. Under these circumstances the difficulties of the operation are not too great, and there is hope of complete elimination of all the tumor

47. Schanz, F. E.: Prostatakrebs, Ztschr. f. urol. Chir. u. Gynäk. **42**:292-307, 1936.

tissue. In the early stage of the disease radical operation is superior to any type of treatment. Surgical removal of the gland is usually followed by roentgen therapy.

Patients who do not present these ideal conditions for operation are usually treated by transurethral electroresection of sufficient extent to relieve urinary obstruction. The advantage of a free flow of urine is more important than the danger of a rapid increase in the growth of the prostate. Patients who are unable to undergo even prostatic resection are treated by an indwelling urethral catheter. Suprapubic drainage was instituted only in the cases in which none of these procedures were possible.

Leiomyoma.—Baretz [48] reported a case of leiomyoma of the prostate gland, making a total of 13 cases of this rare lesion reported in the literature. This type of neoplasm cannot be diagnosed clinically, but it should be borne in mind when a prostate gland, on palpation, is firm, elastic or somewhat unusual in consistence. The growth is benign, and it produces symptoms similar to those of benign hypertrophy of the prostate gland except for increased rectal symptoms. It can be distinguished from benign hyperplasia or sarcoma only by histologic study. It may involve only a small portion of the gland or may have entirely replaced it.

Cysts.—Emmett and Braasch [49] stated that the most common cyst of the prostate gland is the simple retention cyst. This type of cyst is probably produced by obstruction to drainage of the normal prostatic acini with subsequent dilatation or by the coalescing of smaller cysts by means of rupture of the wall of an adjacent cyst. Small symptomless prostatic cysts, which are 0.5 cm. in diameter or smaller, are rather common. Most prostatic cysts never produce symptoms. Emmett and Braasch collected all cases of prostatic cyst reported in the literature since 1925 and summarized them. A series of 14 cases is reported in which prostatic cysts 0.75 cm. in diameter or larger have been encountered.

Diverticulitis.—Heitz-Boyer,[50] on the basis of a complicated case, demonstrated the value of cystography and urethrography in the diagnosis and treatment of severe diverticulitis of the prostate gland.

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48. Baretz, L. H.: Leiomyoma of the Prostate, J. Urol. **35**:664-667 (June) 1936.

49. Emmett, J. L., and Braasch, W. F.: Cysts of the Prostate Gland, J. Urol. **36**:236-249 (Sept.) 1936.

50. Heitz-Boyer, M.: Observation type d'un cas complexe de maladie diverticulaire, à forme de prostatite chronique hypertrophianta; avec opération et guérison des multiples accidents, J. d'urol. **41**:369-387 (April) 1936.

Intense chronic inflammation of the entire prostatic urethra was present, and manifestations of peridiverticulitis leading to chronic prostatitis had been superimposed. The prostatitis was of both the sclerotic and the hypertrophic type and caused the patient to drag out a miserable existence. Urethroscopy revealed the orifice of the diverticulum, rather high up and at the left of the verumontanum; from this opening fibrinous agglomerations, a sort of "diverticular expectoration," were expelled from time to time. Above the verumontanum there was a depression forming a kind of "grotto." Cystoscopy revealed stenosis of the neck of the bladder with a columnar effect, numerous depressions appearing between the columns, while the two urethral orifices were widely dilated. As a result of this complex pathologic condition, retention of urine had caused dilatation of the kidneys, the pelves of which were two or three times normal size, and colon bacilli were present.

Endo-urethral treatment was carried out, consisting first of the exenteration of the diverticulum and the establishment of a wide communication in the prostatic cavity, after which the neck of the bladder was resected. As a result of operation the patient now urinates normally, there is no residual urine and the exaggerated contractility of the muscle of the bladder and the stenosis of the neck of the bladder have disappeared. The vesicoprostatic junction has been reestablished in its proper funnel shape. The patient is cured functionally as well as anatomically. Heitz-Boyer felt that such a result is a clear demonstration of the value of modern urethroscopic and transurethral treatment.

Intraprostatic Injection.—O'Conor and Ladd [51] reviewed the literature dealing with the clinical procedure of direct injection of medicinal solutions into the prostate gland. All previous authors on this subject have inferred that the rationale of the procedure is based on the direct bactericidal effect of the injected solution for the organisms retained in the prostatic acini and ducts. Encouraging clinical reports on intraprostatic injection of solutions in cases of chronic prostatitis have recently extended and revived the interest in this subject. A careful survey of all these reports failed to reveal any published work in which data were given to show what tissue changes actually occur in animals when these solutions have been injected directly into the prostate gland. The experimental work presented by O'Conor and Ladd demonstrated the effects of simple needling of the dog's prostate gland, the changes after the injection of sterile physiologic solution of sodium chloride, distilled water and solutions of mercurochrome, silvol, metaphen, meroxyl, merthiolate and electrargol (a colloidal suspension of silver).

51. O'Conor, V. J., and Ladd, R. L.: Intraprostatic Injection: An Experimental Study, J. A. M. A. **107**:1185-1188 (Oct. 10) 1936.

The technic of injection was devised to avoid all trauma, and the glands were removed en masse after periods varying from two days to three months.

O'Conor and Ladd concluded that the trauma of simple needling of the normal dog's prostate gland is followed by an inflammatory reaction, with considerable subsequent fibrosis and glandular destruction. All the solutions injected into the prostate glands of a series of 31 dogs brought about relatively uniform changes. These changes varied only in severity and degree. It would appear from these studies that any solution injected into the prostate, whether it is physiologic solution of sodium chloride, distilled water or solution of a so-called antiseptic character, results in marked destruction of the acini, chronic inflammatory changes and marked fibrosis. The clinical benefit reported after this procedure might be attributed more properly to fibrotic replacement of infected glandular areas than to an immediate antiseptic effect at the time of injection.

(To be continued)